Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: Tofacitinib

Stand: August 2016

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Tofacitinib **zur Behandlung der mäßigen bis schweren aktiven rheumatoiden Arthritis**	
Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*siehe „II. Zugelassene Arzneimittel im Anwendungsgebiet“*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	„nicht angezeigt“
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	IQWiG-Beauftragung zu Biologika – Zweitlinientherapie bei rheumatoider Arthritis •Rituximab, Abatacept, Etanercept, Infliximab, Adalimumab, Certolizumab Pegol, Golimumab, Anakinra, Tocilizumab; IQWiG-Abschlussbericht A10-01 veröffentlicht am 26.08.2013 •Therapiehinweise zu Adalimumab, Infliximab, Leflunomid
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Tofacitinib L04AA29 XELJANZ®	**zur Behandlung der mäßigen bis schweren aktiven rheumatoiden Arthritis**
Glukokortikoide	
Betamethason H02AB01 (z.B. Celestamine®)	**Autoimmunerkrankungen/Rheumatologie** […] Aktive rheumatoide Arthritis mit schwerer progredienter Verlaufsform, z. B. schnell destruierend verlaufende Formen und/oder mit extraartikulären Manifestationen […] (Stand: Mai 2011)
Dexamethason H02AB02 (z.B. Dexamethason-ratiopharm®)	**Autoimmunerkrankungen/Rheumatologie** […] Aktive rheumatoide Arthritis mit schwerer progredienter Verlaufsform, z. B. schnell destruierend verlaufende Formen und/oder mit extraartikulären Manifestationen […] (Stand: Juli 2015)
Methylprednisolon H02AB04 (z.B. Urbason®)	Erkrankungen, die einer systemischen Therapie mit Glukokortikoiden bedürfen. Hierzu gehören je nach Erscheinungsform und Schweregrad zum Beispiel:: **Rheumatische Erkrankungen**: - Aktive rheumatoide Arthritis mit schweren progredienten Verlaufsformen, z.B. schnell destruierend verlaufende Form und/oder extraartikuläre Manifestationen, […] (Stand: Dezember 2015)
Prednisolon H02AB06 (z.B. Decortin H®)	angezeigt zur Behandlung von Erkrankungen, die einer systemischen Therapie mit Glucocorticoiden bedürfen. Hierzu gehören je nach Erscheinungsform und Schweregrad (…):Decortin H wird angewendet bei Erwachsenen, Kindern aller Altersgruppen und Jugendlichen. […] **Rheumatologie:** […] - aktive rheumatoide Arthritis (…) mit schweren progredienten Verlaufsformen, z. B. destruierend verlaufende Formen (…) und/oder extraartikulären Manifestationen (…) […] (Stand: Oktober 2014)
Prednison H02AB07 (z.B. Prednison-	ist angezeigt zur Behandlung von Erkrankungen, die einer systemischen Therapie mit Glucocorticoiden bedürfen. Hierzu gehören je nach Erscheinungsform und Schweregrad: **Rheumatologie:**

II. Zugelassene Arzneimittel im Anwendungsgebiet	
ratiopharm®)	- […] - Aktive rheumatoide Arthritis (…) mit schweren progredienten Verlaufsformen, z. B. schnell destruierend verlaufende Form (…) und/oder extraartikuläre Manifestationen (…) […] (Stand: September 2014)
Klassische (synthetische) DMARDs (Basistherapeutika)	
Chloroquinphosphat P01BA01 Resochin®	Chronische Polyarthritis (rheumatoide Arthritis) einschließlich juveniler chronischer Arthritis. […] (Stand: November 2013)
Hydrochloroquin-sulfat P01BA02 Quensyl®	Rheumatoide Arthritis. […] (Stand: September 2015)
Leflunomid L04AA13 Arava®	Leflunomid ist ein antirheumatisches Basistherapeutikum („disease modifying antirheumatic drug“ (DMARD)) zur Behandlung von Erwachsenen mit: • aktiver rheumatoider Arthritis, […] (Stand: Dezember 2015)
Methotrexat M01CX01 Lantarel®	Schwere Formen der aktiven rheumatoiden Arthritis (chronischen Polyarthritis) a) wenn eine Therapie mit anderen Basistherapeutika oder mit nicht-steroidalen Antiphlogistika (non-steroidal anti-inflammatory drugs, NSAIDs) nicht ausreichend wirksam ist oder nicht vertragen wird. b) bei primär besonders aggressiv verlaufenden („malignen“) Formen der rheumatoiden Arthritis (chronischen Polyarthritis) […] (Stand: Juni 2016)
Sulfasalazin M01CX02 Azulfidine RA®	Behandlung der aktiven rheumatoiden Arthritis (chronische Polyarthritis) des Erwachsenen. […] (Stand: Juni 2016)
Sonstige	
Azathioprin L04AX01 Zytrim®	Azathioprin ist in Fällen der folgenden Erkrankungen bei Patienten, die Steroide nicht vertragen, die steroidabhängig sind oder bei denen trotz hochdosierter Behandlung mit Steroiden keine ausreichende oder nachhaltige therapeutische Wirkung erzielt werden kann, angezeigt: - schwere akute rheumatoide Arthritis, die nicht mit einer weniger toxischen Basis-Therapie (disease-modifying anti-rheumatic drugs - DMARD) kontrolliert werden kann […] (Stand: August 2013)
Ciclosporin L04AD01 Deximune®	Rheumatoide Arthritis: Behandlung von schwerer, aktiver rheumatoider Arthritis. […] (Stand: Dezember 2015)

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Natriumaurothio-malat , M01CB01 Tauredon®	Chronische Polyarthritis (rheumatoide Arthritis) (Stand: November 2012)
Penicillamin M01CC01 Metalcaptase®	Chronische Polyarthritis rheumatica […] (Stand: Dezember 2014)
biologische DMARDs 1. TNF-Inhibitoren	
Adalimumab L04AB04 Humira®	- Rheumatoide Arthritis Humira ist in Kombination mit Methotrexat indiziert zur • Behandlung der mäßigen bis schweren aktiven rheumatoiden Arthritis bei erwachsenen Patienten, die nur unzureichend auf krankheitsmodifizierende Antirheumatika, einschließlich Methotrexat, angesprochen haben. • Behandlung der schweren, aktiven und progressiven rheumatoiden Arthritis bei Erwachsenen, die zuvor nicht mit Methotrexat behandelt worden sind. Humira kann im Falle einer Unverträglichkeit gegenüber Methotrexat, oder wenn die weitere Behandlung mit Methotrexat nicht sinnvoll ist, als Monotherapie angewendet werden. Humira reduziert in Kombination mit Methotrexat das Fortschreiten der radiologisch nachweisbaren strukturellen Gelenkschädigungen und verbessert die körperliche Funktionsfähigkeit. […] (Stand: Mai 2016)
Certolizumab Pegol L04AB05 Cimzia®	Rheumatoide Arthritis Cimzia ist in Kombination mit Methotrexat (MTX) angezeigt für: • die Behandlung der mittelschweren bis schweren, aktiven rheumatoiden Arthritis (RA) bei erwachsenen Patienten, wenn das Ansprechen auf langwirksame Antirheumatika (Disease-Modifying Antirheumatic Drugs [DMARDs]) einschließlich MTX ungenügend war. • In Fällen von Unverträglichkeit gegenüber MTX oder wenn die Fortsetzung der Behandlung mit MTX ungeeignet ist, kann Cimzia als Monotherapie verabreicht werden. • die Behandlung der schweren, aktiven und fortschreitenden RA bei Erwachsenen, die bisher nicht mit MTX oder anderen DMARDs behandelt wurden. Für Cimzia wurde gezeigt, dass es bei gemeinsamer Verabreichung mit Methotrexat das Fortschreiten von radiologisch nachweisbaren Gelenkschäden reduziert und die körperliche Funktionsfähigkeit verbessert. […] (Stand: Dezember 2015)
Etanercept L04AB01 (z.B. Enbrel®)	Rheumatoide Arthritis Enbrel ist in Kombination mit Methotrexat zur Behandlung der mittelschweren bis schweren aktiven rheumatoiden Arthritis bei Erwachsenen indiziert, wenn das Ansprechen auf Basistherapeutika, einschließlich Methotrexat (sofern nicht kontraindiziert), unzureichend ist. Enbrel kann im Falle einer Unverträglichkeit gegenüber Methotrexat oder wenn eine Fortsetzung der Behandlung mit Methotrexat nicht

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	möglich ist, als Monotherapie angewendet werden. Enbrel ist ebenfalls indiziert zur Behandlung der schweren, aktiven und progressiven rheumatoiden Arthritis bei Erwachsenen, die zuvor nicht mit Methotrexat behandelt worden sind. […] (Stand: April 2016)
Infliximab L04AB02 (z.B. Remicade®)	Rheumatoide Arthritis Remicade ist in Kombination mit Methotrexat indiziert zur: Reduktion der Symptomatik und Verbesserung der körperlichen Funktionsfähigkeit bei: • erwachsenen Patienten mit aktiver Erkrankung, die nur unzureichend auf krankheitsmodifizierende Antirheumatika (DMARDs), einschließlich Methotrexat, angesprochen haben. • Methotrexat-naive, erwachsene Patienten oder erwachsene Patienten, die nicht mit anderen DMARDs vorbehandelt wurden, mit schwergradiger, aktiver und fortschreitender Erkrankung. Bei diesen Patienten wurde anhand von radiologischen Untersuchungen eine Reduktion der Progressionsrate der Gelenkschäden nachgewiesen […] (Stand: September 2015)
Golimumab L04AB06 Simponi®	Rheumatoide Arthritis (RA) Simponi ist in Kombination mit Methotrexat (MTX) indiziert zur: • Behandlung der mittelschweren bis schweren aktiven rheumatoiden Arthritis bei Erwachsenen, wenn das Ansprechen auf eine Therapie mit krankheitsmodifizierenden Antirheumatika (DMARD), einschließlich MTX, unzureichend gewesen ist. • Behandlung der schweren, aktiven und progredienten rheumatoiden Arthritis bei Erwachsenen, die zuvor nicht mit MTX behandelt worden sind. Es wurde gezeigt, dass Simponi in Kombination mit MTX die in Röntgenaufnahmen bestimmte Progressionsrate von Gelenkschäden verringert und die körperliche Funktionsfähigkeit verbessert. […] (Stand: November 2015)
biologische DMARDs 2. Sonstige	
Abatacept L04AA24 Orencia®	*CTLA-4-Analogon zur Blockade der T-Zellaktivierung* Rheumatoide Arthritis ORENCIA ist in Kombination mit Methotrexat (MTX) indiziert zur Behandlung der mäßigen bis schweren aktiven Rheumatoiden Arthritis bei Erwachsenen, die unzureichend auf eine vorangegangene Behandlung mit einem oder mehreren krankheitsmodifizierenden Antirheumatika (DMARDs), einschließlich Methotrexat oder eines Tumornekrosefaktor (TNF)-alpha-Inhibitors ansprachen. Abatacept reduziert in Kombination mit Methotrexat die Progression der Gelenkschädigung und verbessert die körperliche Funktionsfähigkeit. (Stand: April 2016)
Anakinra L04AC03 Kineret®	*IL-1β-Antagonist* Kineret ist bei Erwachsenen zur Behandlung der Symptome der rheumatoiden Arthritis (RA) in Kombination mit Methotrexat indiziert, die nur unzureichend auf Methotrexat allein ansprechen. […] (Stand: März 2016)
Rituximab L01XC02 MabThera® i.v.	*Anti-CD20-Antikörper* Rheumatoide Arthritis MabThera in Kombination mit Methotrexat ist für die Behandlung erwachsener Patienten mit schwerer, aktiver rheumatoider Arthritis

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	angezeigt, die ungenügend auf andere krankheitsmodifizierende Antirheumatika (DMARDs) einschließlich einer oder mehrerer Therapien mit Tumornekrosefaktor (TNF)- Hemmern angesprochen oder diese nicht vertragen haben. […] (Stand: Mai 2016)
Tocilizumab L04AC07 RoActemra®	*IL-6-Antagonist* RoActemra ist, in Kombination mit Methotrexat (MTX), indiziert für: • die Behandlung der schweren, aktiven und progressiven rheumatoiden Arthritis (RA) bei Erwachsenen, die zuvor nicht mit Methotrexat behandelt worden sind. • die Behandlung erwachsener Patienten mit mäßiger bis schwerer aktiver rheumatoider Arthritis, die unzureichend auf eine vorangegangene Behandlung mit einem oder mehreren krankheitsmodifizierenden Antirheumatika (DMARDs) oder Tumornekrosefaktor (TNF)-Inhibitoren angesprochen oder diese nicht vertragen haben. RoActemra kann bei diesen Patienten als Monotherapie verabreicht werden, falls eine Methotrexat-Unverträglichkeit vorliegt oder eine Fortsetzung der Therapie mit Methotrexat unangemessen erscheint. […] (Stand: Juli 2015)

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie (zVT)

Inhalt

Indikation für die Recherche

Zur Behandlung der mittelschweren bis schweren aktiven rheumatoiden Arthritis bei Erwachsenen:
a) in Kombination mit Methotrexat (MTX), wenn das Ansprechen auf MTX unzureichend ist.
b) als Monotherapie bei Unverträglichkeit gegenüber MTX oder wenn eine Fortsetzung der Behandlung mit MTX nicht möglich ist

Berücksichtigte Wirkstoffe/Therapien:

siehe Unterlage zur Beratung in AG: Übersicht zVT, Tabellen „I. Zweckmäßige Vergleichstherapie“ und „II. Zugelassene Arzneimittel im Anwendungsgebiet.“

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation

„Rheumatoide Arthritis**“** durchgeführt. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, Clinical Evidence, G-BA, GIN, IQWiG, NGC, NICE, TRIP. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Bei der Recherche wurde keine Sprachrestriktion vorgenommen. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche erfolgte am 13.10.2015 (Suchzeitraum eingeschränkt auf die letzten 5 Jahre) und ergab 980 Quellen. Eine Folgerecherche am 14.07.2016 (Suchzeitraum eingeschränkt auf Oktober 2015 bis 14.07.2016) ergab 146 Quellen. Die Treffer wurden nach Themenrelevanz und methodischer Qualität gesichtet. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Für die Synopse wurden nur die Quellen aus den letzten 5 Jahren berücksichtigt. Insgesamt ergab dies **47** Dokumente, die in die synoptische Evidenz-Übersicht aufgenommen wurden.
Die eingeschlossenen Dokumente der Folgerecherche sind farblich markiert.

Abkürzungen

ACR	American College of Rheumatology
AE	adverse event
AHRQ	Agency for Health Research and Quality
AIMS	Abatacept in Inadequate responders to Methotrexate
ATB	absolute treatment benefit
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BSR	British Society for Rheumatology
BUC	bucillamine
CCT	controlled clinical trials
CDER	Center for Drug Evaluation and Research
CI	confidence intervall
CRP	C-reactive protein
CSA	cyclosporine
DAHTA	Deutsche Agentur für Health Technology Assessment
DAS	Disease Activity Score
DAS28	Disease Activity Score 28
DMARD	Disease modifying anti-rheumatic drug
EMS	early morning stiffness
ES	Erosion Score
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
HAQ	Health Assessment Questionnaire
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
IR	inadaequate response
JSNS	Joint Space Narrowing Score
KI	Konfidenzintervall
KQ	key question
LEF	Leflunomid
MCMC	Markov chain Monte Carlo techniques
MRI	magnetic resonance imaging
MTC	Mixed-treatment comparisons

MTX	Methotrexate
NGC	National Guideline Clearinghouse
NICE	National Institute for Health and Care Excellence
NSAID	non-steroidal anti-inflammatory drug
PARPR	percentage of the annual radiographic progression rate
PBO	Placebo
QALY	Quality Adjusted Life Years
RA	rheumatoid arthritis
RCT	Randomized controlled trial
RR	risk ratio
SAE	serious adverse event
SASP	Sulfasalazine
SD	standard deviation
SF-36	Short Form 36
SIGN	Scottish Intercollegiate Guidelines Network
SJC	swollen joint count
SSZ	sulfasalazine
TNF	tumour necrosis factor
TRIP	Turn Research into Practice Database
TSS	Total Sharp Score
VAS	Visual Analog Scale

IQWiG-Berichte/G-BA-Beschlüsse

IQWiG, 2013 [18]. Biotechnologisch hergestellte Arzneimittel in der Zweitlinientherapie bei der rheumatoiden Arthritis.	**Fragestellung/Ziele:** Die Nutzenbewertung einer Behandlung mit biotechnologisch hergestellten Arzneimitteln im Vergleich untereinander, die Nutzenbewertung einer Behandlung mit biotechnologisch hergestellten Arzneimitteln im Vergleich zu einer Behandlung mit nicht biotechnologisch hergestellten Arzneimitteln, die Nutzenbewertung einer Behandlung mit biotechnologisch hergestellten Arzneimitteln im Vergleich zu einer Behandlung ohne Therapieerweiterung (mit oder ohne Placebo-Kontrolle), jeweils als **Zweitlinientherapie** bei Patienten mit RA. **Population:** Erwachsene mit RA ***Intervention:*** Biotechnologisch hergestellte Arzneimittel (bDMARDs) • Abatacept (Orencia®) • Adalimumab (Humira®) • Anakinra (Kineret®) • Certolizumab pegol (Cimzia®) • Etanercept (Enbrel®) • Golimumab (Simponi®) • Infliximab (Remicade®) • Rituximab (MabThera®) • Tocilizumab (RoActemra®) ***Kontrolle:*** Behandlung mit einem anderen bDMARD oder einem nicht biotechnologisch hergestellten Antirheumatikum oder die Behandlung ohne Therapieerweiterung (mit oder ohne Placebokontrolle) Die Anwendung der in den Studien eingesetzten Prüf- und Vergleichsinterventionen musste im Rahmen des für Deutschland gültigen Zulassungsstatus erfolgen. ***Endpunkte***: (siehe Anlage 1) • Remission • Symptomatik der RA (insbesondere Schmerz, Fatigue, Morgensteifigkeit) • Strukturelle Gelenkveränderungen (wie Deformitäten, Versteifungen, Kontrakturen) • Körperlicher Funktionsstatus einschließlich Aktivitäten des täglichen Lebens • Soziales Funktionsniveau (Teilhabe am beruflichen und sozialen Leben) • Gesundheitsbezogene Lebensqualität • Gesamtmortalität • unerwünschte Arzneimittelwirkungen ***Recherchezeitraum/Aktualität*** • Recherche bis 09/2010 Einschluss nur von RCT, mindestens 6 Monate Studiendauer, dabei auch Herstelleranfragen und Studienregister-Recherche

Ergebnis /Fazit:

Tabelle 1: Paarweise Vergleiche der Interventionen mit Studien- und Patientenzahl

Intervention + MTX[a]	Kontrolle + MTX[a]	Anzahl der Studien	Anzahl der Patienten[b]
Abatacept	Placebo	6	2679
Adalimumab	Placebo	6	1508
Anakinra	Placebo	2	1653
Certolizumab pegol	Placebo	4	1286
Etanercept	Placebo	2	548
Etanercept[c] (MTX-Intoleranz)	Sulfasalazin[c]	1	71
Etanercept[c] (Patienten mit schwerer aktiver und progressiver RA)	MTX[c]	1	41
Golimumab (keine Vorbehandlung mit TNF-α-Inhibitoren)	Placebo	2	401
(Vorbehandlung mit TNF-α-Inhibitoren)	Placebo	1	205
Infliximab	Placebo	1	174
Rituximab (keine Vorbehandlung mit Rituximab)	Placebo	1	520
(nach fehlendem Ansprechen auf einen Zyklus Rituximab)	Placebo	1	475
Tocilizumab (mehrheitlich ohne Vorbehandlung mit TNF-α-Inhibitoren)	Placebo	5	2836
(Vorbehandlung mit TNF-α-Inhibitoren)	Placebo	1	335
Direktvergleich:			
Tocilizumab[c] (Patienten, die für eine Weiterbehandlung mit MTX nicht geeignet waren)	Adalimumab[c]	1	326
Summe:		35	13 058

a: wenn nicht anders angegeben
b: relevante Populationen für die vorliegende Bewertung
c: Monotherapie
MTX: Methotrexat, RA: rheumatoide Arthritis, TNF: Tumornekrosefaktor

Hinweis: Es wurden lediglich direkte Vergleiche extrahiert. Auf eine Darstellung der Placebovergleiche wurde verzichtet.

Anzahl relevanter Studien/Patienten: 3 (n= 438)

Abatacept; Adalimumab; Anakinra; Certolizumab pegol; Golimumab; Infliximab; Rituximab; Tocilizumab: *Ergebnisse nur im Vergleich gegen Placebo*

Etanercept
Ergebnisse im Vergleich gegen Placebo sowie:

Für Etanercept gibt es (im Vergleich zu Sulfasalazin) bei Patienten mit MTX-Intoleranz

- einen Anhaltspunkt für einen Zusatznutzen von Etanercept gegenüber Sulfasalazin hinsichtlich der Symptomatik der RA bezogen auf schmerzhafte Gelenke und geschwollene Gelenke, Schmerz, die globale Einschätzung der Krankheitsaktivität durch den Patienten und die allgemeine Gesundheit sowie hinsichtlich der Morgensteifigkeit und des körperlichen Funktionsstatus,

	• keinen Beleg für einen Zusatznutzen hinsichtlich der Remission und hinsichtlich der strukturellen Gelenkveränderungen (wie Deformitäten, Versteifungen, Kontrakturen), des sozialen Funktionsniveaus und der gesundheitsbezogenen Lebensqualität aufgrund fehlender Daten • keinen Beleg für einen geringeren oder größeren Schaden durch eine der beiden Prüfinterventionen im Hinblick auf die Gesamt-mortalität und im Hinblick auf schwerwiegende unerwünschte Ereignisse, Studienabbrüche aufgrund von unerwünschten Ereignissen, die Gesamtrate der unerwünschten Ereignisse, schwerwiegende Infektionen und die Gesamtrate der Infektionen. Für Etanercept gibt es (im Vergleich zu MTX) bei Patienten mit schwerer aktiver und progressiver RA • einen Anhaltspunkt für einen Zusatznutzen von Etanercept gegenüber MTX hinsichtlich der Remission, hinsichtlich der Symptomatik der RA bezogen auf schmerzhafte Gelenke, geschwollene Gelenke, Schmerz, die globale Einschätzung der Krankheitsaktivität durch den Patienten, die allgemeine Gesundheit sowie die Morgensteifigkeit, • keinen Beleg für einen Zusatznutzen hinsichtlich der strukturellen Gelenkveränderungen (wie Deformitäten, Versteifungen, Kontrakturen) aufgrund fehlender Daten, hinsichtlich des körperlichen Funktionsstatus, des sozialen Funktionsniveaus und der gesundheitsbezogenen Lebensqualität jeweils aufgrund fehlender Daten • keinen Beleg für einen geringeren oder größeren Schaden durch eine der beiden Prüfinterventionen im Hinblick auf die Gesamt-mortalität und im Hinblick auf schwerwiegende unerwünschte Ereignisse, Studienabbrüche aufgrund von unerwünschten Ereignissen, die Gesamtrate der unerwünschten Ereignisse, schwerwiegende Infektionen und die Gesamtrate der Infektionen. Für Tocilizumab im Vergleich zu Adalimumab bei Patienten, die für eine Weiterbehandlung mit MTX nicht geeignet waren, gibt es • einen Hinweis auf einen Zusatznutzen hinsichtlich der Remission, • keinen Beleg für einen Zusatznutzen hinsichtlich der Symptomatik der RA bezogen auf schmerzhafte Gelenke, geschwollene Gelenke, Schmerz, die globale Einschätzung der Krankheitsaktivität durch den Patienten und Fatigue, hinsichtlich des körperlichen Funktionsstatus und hinsichtlich der gesundheitsbezogenen Lebensqualität – für strukturelle Gelenkveränderungen (wie Deformitäten, Versteifungen, Kontrakturen) und für das soziale Funktionsniveau lagen keine Daten vor, • keinen Beleg für einen größeren bzw. geringeren Schaden im Hinblick auf die Gesamtmortalität, schwerwiegende unerwünschte Ereignisse, Studienabbrüche aufgrund von unerwünschten Ereignissen, die Gesamtrate der unerwünschten Ereignisse, schwerwiegende Infektionen und die Gesamtrate der Infektionen.
G-BA, 2007 [11]. Bekanntmachung eines Beschlusses des	**Wirkstoff: Leflunomid (Arava®)** **Indikation: Rheumatoide Arthritis** • In fortgeschritteneren Krankheitsstadien hat sich Leflunomid als ähnlich wirksam erwiesen wie MTX oder SSZ. Unter wirtschaftlichen Gesichtspunkten bietet es sich als Mittel der zweiten oder dritten Wahl an. Bei therapierefraktären Verläufen kann sein Einsatz erwogen werden bevor auf einen TNF Alpha Blocker umgestellt wird. Die

Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie in Anlage 4: Therapiehinweis zu Leflunomid.	Überlegenheit einer Kombination von Leflunomid mit einem Tumornekrosefaktor (TNF) Alpha Blocker gegenüber einer TNF Alpha Blocker Monotherapie ist durch randomisierte kontrollierte Studien nicht belegt. Vergleichende Studien zur Kombination von TNF Alpha Blockern mit MTX gibt es nicht. Es ist bisher kein TNF Alpha Blocker explizit für eine Kombinationstherapie mit Leflunomid zugelassen. • Bei ungesichertem Nutzen und erhöhtem Risiko für toxische Nebenwirkungen ist eine Kombinationstherapie von Leflunomid mit TNF Alpha Blockern in der Regel unwirtschaftlich. Für den Fall einer Unverträglichkeit von MTX auch in niedrigeren Dosierungen bzw. Vorliegen von Kontraindikationen, die den Einsatz von MTX ausschließen, sind die TNF Alpha Inhibitoren Adalimumabund Etanercept auch als Monotherapie zugelassen. Bei Versagen einer Therapie mit TNF Alpha Blockern stehen für diese Situation zugelassene Biologicals wie Abatacept oder Rituximab zur Verfügung.
G-BA, 2007 [12]. Bekanntmachung eines Beschlusses des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie/AMR in Anlage 4: Therapiehinweis zu Adalimumab	**Wirkstoff: Adalimumab (zum Beispiel Humira®)** **Indikation Rheumatoide Arthritis und Psoriasis-Arthritis** • Die Behandlung mit TNF-alpha-Hemmern stellt dabei eine Alternative zur Reduktion der Symptomatik und Verbesserung der körperlichen Funktionsfähigkeit bei Patienten mit aktiver Rheumatoider Arthritis oder Arthritis psoriatica dar, wenn eine Therapie mit allen individuell indizierten DMARDs und deren Kombinationen, mindestens jedoch 2 einschließlich Methotrexat (MTX) — soweit keine Kontraindikationen dafür vorliegen — bis zur individuell angezeigten Höchstdosis (in der Regel 20 bis 25 mg pro Woche, ggf. als Injektion und ggf. Folsäure- bzw. Folinsäurepräparate), erfolglos geblieben ist. Diese müssen lange genug (in der Regel je nach DMARD mindestens jeweils 3 bis 6 Monate) in adäquater Dosis und unter fachlich kompetenter Überwachung eingesetzt worden sein. • Für einen breiten Einsatz von Adalimumab als erstes DMARD bei neu diagnostizierter Rheumatoider Arthritis fehlen derzeit u. a. evaluierte prädiktive Faktoren für den Krankheitsverlauf, die eine ausreichend sichere Auswahl der Patienten mit schwerer progressiver Arthritis in frühen Krankheitsstadien ermöglichen würde. In der Regel ist die Primäranwendung daher bei der derzeitigen Studienlage nicht angezeigt. Bei seltenen individuellen Besonderheiten (Kontraindikationen gegen alle DMARDs oder hohe Krankheitsprogression) kann ein frühzeitiger Einsatz von TNF-alpha-Hemmern angemessen sein. • Bei der Wahl eines TNF-alpha-Hemmers können aus medizinisch-therapeutischer Sicht aufgrund der derzeitigen Studienlage oder evidenzbasierter Leitlinien bei der Indikation Rheumatoide Arthritis keine allgemeinen Prioritäten gesetzt werden. • Bei der Indikation Psoriasis-Arthritis ist der unterschiedliche Zulassungsstatus bzgl. der Hautmanifestation der Psoriasis zu beachten, insbesondere da die Zulassung von Etanercept und Infliximab die Anwendung bei Arthritis psoriatica und bei therapieresistenter mittelschwerer bis schwerer Plaque psoriasis abdeckt. Die voraussichtlichen Therapiekosten für das ausgewählte Präparat stellen damit bei Beginn einer TNF-alpha- Therapie den wesentlichen Gesichtspunkt bei der Produktwahl dar. Davon kann abgewichen werden, wenn individuelle klinische Faktoren (z. B. Neben- und Wechselwirkungen) bzw. die spezifischen Eigenschaften oder die Anwendungsmodalitäten des Arzneimittels eine nachvollziehbare

	Kontraindikation darstellen oder die bevorzugte Anwendung im Einzelfall begründen. Auch die Praxisausstattung (z. B. Lagerungsmöglichkeit für Infusionen und Nachüberwachung beim Einsatz von Infliximab) begründet keine unwirtschaftliche Produktwahl. • Ein Ansprechen auf die Therapie ist bereits nach 1 bis 2 Wochen zu erwarten. Soweit auch nach 3 Monaten kein deutliches klinisches Ansprechen (klinische Symptomatik, DASScore, Labor) zu verzeichnen ist, ist die Therapie mit Adalimumab abzusetzen. • Eine Dosiserhöhung durch Verkürzung des Intervalls auf wöchentlich 40 mg bei Patienten mit einer Adalimumab-Monotherapie ist in der Regel unwirtschaftlich.
G-BA, 1999 [13]. Beschluss über eine Änderung der Anlage 4 der Richtlinien des Bundesausschusses der Ärzte und Krankenkassen über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (Arzneimittel-Richtlinien/AMR) - Etanercept, Leflunomid	**Wirkstoff:** Etanercept (z.B. Enbrel®) **Wirksamkeit** Etanercept wurde in mehreren klinischen Phase II und Phase III Studien an erwachsenen Patienten mit rheumatoider Arthritis allein oder in Kombination mit Methothrexat erprobt. Gegenüber Plazebo zeigte sich eine signifikante Verbesserung hinsichtlich der Entzündungsaktivität und der Funktionseinschränkungen. Die Wirksamkeit der Therapie zeigte sich nach ein bis zwei Wochen und war dosisabhängig. Nach Absetzen der Therapie kam es überwiegend innerhalb von 4 Wochen zu einem Wiederaufflammen der Symptome. Unter der Kombinationsbehandlung mit Etanercept und Methotrexat konnte eine klinische Besserung auch bei Patienten erreicht werden, die zuvor auf Methotrexat allein nicht oder unzureichend angesprochen hatten. Es liegen bisher keine Erfahrungen zur Langzeitbehandlung über mehr als 36 Monate vor. Weiterhin ist offen, ob es sich ausschließlich um eine kurzfristige symptomatische Therapie handelt oder ob Etanercept den natürlichen Krankheitsverlauf mit Destruktion der Gelenke aufhalten kann. **Empfehlungen zur wirtschaftlichen Verordnungsweise** Voraussetzung für den Einsatz von Etanercept als Behandlungsalternative ist das Versagen aller im individuellen therapeutischen Verlauf angemessenen Basismedikationen. Die Erfahrungen mit dem Präparat sind noch begrenzt. Aufgrund der Zytokinhemmung können Langzeitwirkungen bzw. Nebenwirkungen noch nicht abgeschätzt werden. Es ist zu empfehlen, vor Verordnung von Etanercept unter Einbeziehung rheumatologischen Sachverstandes eine strukturierte Zweitmeinung (z. B. Clearingstelle bei der KV) einzuholen.

Cochrane Reviews

Lethaby A et al., 2013 [24]. Etanercept for the treatment of rheumatoid arthritis.	**1. Fragestellung** To update the previous Cochrane systematic review published in 2003 assessing the benefits and harms of etanercept for the treatment of RA. In addition, we also evaluated the benefits and harms of etanercept plus DMARD compared with DMARD monotherapy in those people with RA who are partial responders to methotrexate (MTX) or any other traditional DMARD.
	2. Methodik ***Population:*** Extraktion fokussiert auf Patienten die <u>vorbehandelt</u> sind → What happens to people with rheumatoid arthritis who take etanercept plus traditional DMARDs (methotrexate or sulphasalazine) after they have NOT improved with

	traditional DMARDs alone ***Intervention:*** Etanercept ***Vergleiche/Komparatoren:*** siehe Ergebnisteil ***Endpunkte*** Primär: The set of efficacy measures includes: 1) tender joint count; 2) swollen joint count; 3) patient assessment of pain using 10-cm visual analogue scale or Likert scale; 4) patient global assessment of disease activity; 5) physician global assessment of disease activity using 10-cm visual analogue scale or Likert scale; 6) patient assessment of functional ability as measured by a validated scale such as the Health Assessment Questionnaire (HAQ), which is a standardised, validated scale used in people with arthritis; 7) acute phase reactants such as ESR or CRP; 8) Radiographic bone changes are accepted as part of the core set of disease activity measures in studies of a minimum of 12 months' duration. Sekundär: • health-related quality of life (HRQoL) such as the Short Form (SF)-36, when available; • adverse events (AEs); • withdrawals from the study (total, due to lack of efficacy, due to AEs and death). ***Einschlusskriterien für Primärstudien*:** RCTs or controlled clinical trials (CCTs) (minimum 24 weeks' duration) ***Suchzeitraum***: 1966 bis 2003; 2003 bis 01/2012 (Update) ***Anzahl eingeschlossene Studien/Patienten (Gesamt)*:** 9 (n = 2800) ***Qualitätsbewertung der Studien:*** Cochrane Risk of Bias
	3. Ergebnisdarstellung Allgemein: The trials were **generally of moderate to low risk of bias**, the majority funded by pharmaceutical companies. Follow-up ranged from six months to 36 months. **What happens to people with rheumatoid arthritis who take etanercept plus traditional DMARDs (methotrexate or sulphasalazine) after they have NOT improved with traditional DMARDs alone:** ACR 50 (number of tender or swollen joints and other outcomes such as pain and disability) - 38 more people out of 100 had a 50% improvement in symptoms after six months to three years compared with people taking a DMARD alone (38% absolute improvement). 79 people out of 100 on etanercept plus DMARDs had a 50% improvement in symptoms. 41 people out of 100 on DMARDs alone had a 50% improvement in symptoms Disease activity

	- 22 more people out of 100 were considered to have low disease activity of their rheumatoid arthritis from six months to three years on etanercept with DMARDs (22% absolute improvement). - 46 people out of 100 on etanercept plus DMARDs were considered to have low disease activity of their rheumatoid arthritis. - 24 people out of 100 on DMARDs alone were considered to have low disease activity of their rheumatoid arthritis. <u>Disability</u> - People who took etanercept plus a DMARD rated the change in their disability to be 0.36 points lower on a scale of 0 to 3 after six months to three years compared with people who took a DMARD alone (12% absolute improvement). - People who took etanercept plus a DMARD rated the change in their disability to be between 0.51 and 1.08 on a scale of 0 to 3 after six months to three years. - People who took a DMARD alone rated the change in their disability to be between 0.15 and 0.72 on a scale of 0 to 3 after six months to three years. <u>X-rays of the joints</u> - When all people in all the studies were considered, joint damage improved slightly in those who received combined treatment with etanercept plus DMARD compared with DMARD or etanercept alone after 12 to 36months. Joint damage in people whom DMARDs were not working and received combined treatment with etanercept plus DMARD was similar to those given a DMARD alone, but this result might be due to low numbers of people in this group.
	4. Fazit der Autoren: Etanercept 25mg administered subcutaneously twice weekly together with MTX was more efficacious than either etanercept or MTX monotherapy for ACR50 and it slowed joint radiographic progression after up to three years of treatment for all participants (responders or not). There was no evidence of a difference in the rates of infections between groups.
Ruiz GV et al., 2014 [36]. Certolizumab pegol (CDP870) for rheumatoid arthritis in adults	**1. Fragestellung/Zielsetzung** To assess the clinical benefits and harms of certolizumab pegol (CDP870) in patients with RA who have not responded well to conventional disease-modifying anti-rheumatic drugs (DMARDs).
	2. Methodik **Population:** Adults (18 years of age and older) with RA who have persistent disease activity despite current or previous use of conventional DMARDs. **Intervention:** Certolizumab pegol (CDP870) at any dose **Komparator:** Placebo or any DMARD including other biologic agents used to treat RA **Endpunkte** *Major Endpoints:* • The proportion of patients achieving an ACR50 • Health-related quality of life, such as the Health Assessment Questionnaire (HAQ) or Short Form Health Survey (SF-36) • Disease Activity Score (DAS28 or other versions of DAS) • Radiological changes (erosion score (ES), modified total Sharp score, joint

	space narrowing) • Serious adverse events • All withdrawals • Withdrawals due to adverse events *Minor Endpoints:* • ACR20 and ACR70 • Frequency of adverse events **Suchzeitraum (Aktualität der Recherche):** We searched the Cochrane Central Register of Controlled Trials (The Cochrane Library 2014, Issue 5), MEDLINE, EMBASE, Scopus, TOXLINE,Web of Knowledge; websites of the US Food and Drug Administration (FDA) and EuropeanMedicines Evaluation Agency (EMEA); reference lists of articles; and searched http/clinicaltrials.gov. The searches were updated from 2009 (date of last search for the original review) to 5 June 2014. **Anzahl eingeschlossener Studien/Patienten (Gesamt):** Eleven trials were included in this update. Ten (4324 patients) were included in the pooled analysis for benefits, five more than previously, and 10 (3711 patients) in the pooled analysis for harms, four more trials (1930 patients) than previously. The duration of follow-up varied from 12 to 52 weeks and the range of doses of certolizumab pegol varied from 50 to 400 mg given subcutaneously (sc). In phase III trials, the control was placebo plus MTX in five trials and placebo in four trials. **Qualitätsbewertung der Studien:** Cochrane Risk of Bias zur Bewertung des Verzerrungsrisikos auf Einzelstudienebene, GRADE zur Bewertung der overall quality of evidence
	3. Ergebnisdarstellung **Quality of Evidence** • The quality of the evidence found in the trials included in this review was high. Studies had high standards for treatment allocation, concealment and blinding, but there may have been a risk of attrition bias. • The risk of bias was low and the quality of evidence was downgraded to moderate because of high rates of dropouts (> 20%) in most of the trials. We did not find any problems with inconsistency, indirectness, imprecision or publication bias. **Wirksamkeit:** • Statistically significant improvements were observed at 24 weeks with the approved dose of 200 mg certolizumab pegol every other week, in 1) American College of Rheumatology (ACR) 50% improvement: 27% absolute improvement (95% CI 20% to 33%), risk ratio (RR) 3.80 (95% CI 2.42 to 5.95); moderate quality of evidence 2) the Health Assessment Questionnaire (HAQ): -12% absolute improvement (95% CI -9% to -14%), mean difference (MD) - 0.35 (95% CI -0.43 to -0.26) (scale 0 to 3); moderate quality of evidence 3) Disease Activity Score (DAS) remission improvement: absolute improvement 11% (95% CI 8% to 15%), RR 8.47 (95% CI 4.15-17.28); 4) radiological changes: erosion score (ES) absolute improvement -0.29% (95% CI -0.42% to -0.17%), MD -0.67 (95% CI -0.96 to -0.38) (scale 0 to 230); moderate quality of evidence **Sicherheit:**

	• Serious adverse events were statistically significantly more frequent for certolizumab pegol (200 mg every other week) with an absolute rate difference of 4% (95% CI 2% to 6%), Peto odds ratio (OR) 1.77 (95% CI 1.27 to 2.46).; moderate quality of evidence • There was a statistically significant increase in all withdrawals in the placebo groups (for all doses and all follow-ups) with an absolute rate difference of -34% (95% CI -18% to -50%), RR 0.42 (95% CI 0.36 to 0.50); moderate quality of evidence • There was a statistically significant increase in all withdrawals due to adverse events in the certolizumab groups (for all doses and all follow-up) with an absolute rate difference of 2% (95% CI 1% to 3%), Peto OR 1.66 (95% CI 1.15 to 2.37). moderate quality of evidence
	4. Fazit der Autoren: The results and conclusions did not change from the previous review. There is moderate-level evidence from randomised controlled trials that certolizumab pegol alone or combined with methotrexate is beneficial in the treatment of RA. Adverse events were more frequent with active treatment. We found a potential risk of serious adverse events.
Lopez-Olivo MA et al., 2015 [26]. Rituximab for rheumatoid arthritis	**1. Fragestellung** To evaluate the benefits and harms of rituximab for the treatment of RA.
	2. Methodik ***Population*** adult RA patients ***Intervention:*** rituximab as monotherapy or in combination with any DMARDs (traditional or biologic) ***Komparator:*** placebo or other DMARDs (traditional or biologic) ***Endpunkte:*** response of RA defined by ACR, WHO and ILAR core set of disease activity measures • ACR50, ACR20, ACR70 • Disease remission • Functional status • Radiographic progression • QoL • Withdrawal due to AE • AE, SAE ***Suchzeitraum (Aktualität der Recherche):*** up to Jan 2014 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 8 (n=2720) ***Qualitätsbewertung der Studien*** Cochrane Risk of Bias
	3. Ergebnisdarstellung Study populations: • Patients intolerant to at least 1 TNF inhibitor: 1 study • Inadequate response to MTX/DMARDs: 5 studies • Previous MTX and either eta or ada: 1 study • No previous MTX/DMARD treatment:1 study The level of evidence ranged from low to high, but was rated as moderate for most outcomes <u>Rituximab + MTX vs MTX alone</u> (5 studies, 1664 patients)

	At w24 (4 studies) • ACR50: RR 3.3 (95% CI 2.3 to 4.6) • ACR20: RR 2.2 (95% CI 1.9 to 2.7) • ACR70: RR 3.9 (95% CI 1.8 to 8.3) • clinically meaningful improvement in the Health Assessment Questionnaire (HAQ) (>0.22): RR 1.6 (95%CI 1.2 to 2.1) *At w52* • ACR50: RR 2.2 (95%CI 1.3-4.0) • ACR20 RR 1.53 (95%CI 1.09 to 2.13) • ACR70 RR 1.95 (95%CI 1.53 to 2.49] • ACR90: RR 1.8 (95% CI 1.1 to 3.0) (1 study) • HAQ-MCID=-0.22: RR 1.57 (95%CI 0.71 to 3.44) • clinical remission (Disease Activity Score (DAS) 28 joints < 2.6): RR 2.4 (95%CI 1.7 to 3.5) • SF-36 ○ clinically meaningful improvement in the physical component score (SF-36 PCS ≥ 5): RR 2.0 (95% CI 1.1 to 3.4) ○ clinically meaningful improvement in the mental component score (SF-36 MCS ≥ 5): RR 1.4 (95% CI 1.1 to 1.9) • clinically meaningful improvement in the fatigue score (FACIT ≥ 4): RR 1.6 (95% CI 1.0 to 2.5) *at w104* • sig. superiority of combination based on ACR50, 70 and 90 response, HAQ but not on ACR20 ->**Superiority of combination therapy** Safety: • no statistically significant difference in the rates of withdrawals due to AE or for other reasons in either group. • However, statistically significantly more people receiving the control drug withdrew from the study compared to those receiving rituximab (two 1000 mg doses) in combination with methotrexate at all times (RR 0.40, 95% CI 0.32 to 0.50; RR 0.61, 95% CI 0.40 to 0.91; RR 0.48, 95% CI 0.28 to 0.82; RR 0.58, 95% CI 0.45 to 0.75, respectively). • A greater proportion of patients receiving rituximab (two 1000 mg doses) in combination with methotrexate developed AEs after their first infusion compared to those receiving methotrexate monotherapy and placebo infusions (RR 1.6, 95% CI 1.3 to 1.9); • no statistically significant differences in the rates of SAE <u>Rituximab monotherapy vs MTX monotherapy</u> Superiority of rituximab at w 24 based on ACR response: • ACR20: RR 1.7 (95% CI 1.1 to 2.8) • ACR50: RR 2.6 (95% CI 1.0 to 6.6) These statistically significant differences disappeared at 48 weeks and 104 weeks. In addition, no statistically significant differences between groups were observed on the ACR 70 response rates at 24, 48, and 104 weeks • significant difference in reduction from baseline in the DAS28 at 24weeks

	between rituximab alone and the methotrexate alone group (MD -0.90, 95% CI -1.47 to -0.33) • statistically significant improvement in HAQ scores with rituximab alone compared to methotrexate alone (MD of -0.40 (95% CI -0.65 • to -0.15)) at 24 weeks, but the statistically significant difference disappeared at 48 and 72 weeks
	4. Fazit der Autoren Evidence from eight studies suggests that rituximab (two 1000 mg doses) in combination with methotrexate is significantly more efficacious than methotrexate alone for improving the symptoms of RA and preventing disease progression **5. Hinweise FBMed** Heterogene Patientenpopulation (in Bezug auf Vortherapien) eingeschlossen
Singh JA et al., 2016 [42]. Biologics or tofacitinib for rheumatoid arthritis in incomplete responders to methotrexate or other traditional disease-modifying anti-rheumatic drugs: a systematic review and network meta-analysis.	**1. Fragestellung** To assess the benefits and harms of nine biologics (abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab) and small molecule tofacitinib, versus comparator (MTX, DMARD, placebo (PL), or a combination) in adults with rheumatoid arthritis who have failed to respond to methotrexate (MTX) or other disease-modifying anti-rheumatic drugs (DMARDs), i.e., MTX/DMARD incomplete responders (MTX/DMARD-IR).
	2. Methodik We conducted network meta analysis (NMA) using a Bayesian mixed treatment comparison (MTC) approach, and traditional meta-analysis to determine the effectiveness of treatments com- pared to each other. Population: Adults, 18 years or older, with RA meeting the 1987 American College of Rheumatology (ACR) classification criteria for RA (Arnett 1988) or the 2010 ACR/European League Against Rheumatism (EULAR) classification criteria for RA (Aletaha 2010) and who were MTX/DMARD-experienced (including MTX/DMARD- IR). Intervention / Komparator: Biologics (abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab) or to- facitinib used alone or in combination with traditional DMARD/ other biologics compared to placebo (PL) alone or to PL plus tra- ditional DMARDs or biologics or combinations of DMARDs. Endpunkt: ACR50, RA disease remission, Function measured by HAQ score or modified HAQ calculated as score changes and the proportion achieving minimal clinically important difference on HAQ ≤ 0.22, radiographic progression, Withdrawals due to adverse events, Serious adverse events (SAEs), Cancer Suchzeitraum (Aktualität der Recherche): Systematische Literaturrecherche

	bis 2015 Anzahl eingeschlossene Studien/Patienten (Gesamt): This update included 73 new RCTs for a total of 90 RCTs. 79 RCTs with 32,874 participants provided usable data. Qualitätsbewertung der Studien: Cochrane 'Risk of bias' tool & GRADE approach for both direct and NMA estimates.
	3. Ergebnisdarstellung Qualität der Studien: Few trials were at high risk of bias for blinding of assessors/participants (13% to 21%), selective reporting (4%) or major baseline imbalance (8%); a large number had unclear risk of bias for random sequence generation (68%) or allocation concealment (74%). • Direct evidence (moderate quality → downgraded for inconsistency: biologic+MTX/DMARD was associated with a statistically significant and clinically meaningful improvement in ACR50 versus comparator (RR 2.71 (95% CI: 2.36 to 3.10); absolute benefit 24% more patients (95% CI 19% to 29%), number needed to treat for an additional beneficial outcome (NNTB) = 5 (4 to 6). • NMA estimates for ACR50 in tumor necrosis factor (TNF) biologic+MTX/DMARD (RR 3.23 (95% Crl: 2.75 to 3.79), non-TNF biologic+MTX/DMARD (RR 2.99; 95% Crl 2.36 to 3.74), and anakinra + MTX/DMARD (RR 2.37 (95% Crl 1.00 to 4.70) were similar to the direct estimates. • Direct evidence (moderate quality → downgraded for inconsistency): biologic+MTX/DMARD was associated with a clinically and statistically important improvement in function measured by the Health Assessment Questionnaire (0 to 3 scale, higher = worse function) with a mean difference (MD) based on direct evidence of -0.25 (95% CI -0.28 to -0.22); absolute benefit of -8.3% (95% CI -9.3% to -7.3%), NNTB = 3 (95% CI 2 to 4). • NMA estimates for TNF biologic+MTX/DMARD (absolute benefit, -10.3% (95% Crl -14% to -6.7%) and non-TNF biologic+MTX/DMARD (absolute benefit, -7.3% (95% Crl -13.6% to -0.67%) were similar to respective direct estimates. • Direct evidence (moderate quality → downgraded for inconsistency): biologic+MTX/DMARD was associated with clinically and statistically significantly greater proportion of participants achieving remission in RA (defined by disease activity score DAS < 1.6 or DAS28 < 2.6) versus comparator (RR 2.81 (95% CI, 2.23 to 3.53); absolute benefit 18% more patients (95% CI 12% to 25%), NNTB = 6 (4 to 9)). • NMA estimates for TNF biologic+MTX/DMARD (absolute improvement 17% (95% Crl 11% to 23%)) and non-TNF biologic+MTX/DMARD (absolute improvement 19% (95% Crl 12% to 28%) were similar to respective direct estimates. • Direct evidence (moderate quality → downgraded for inconsistency):

	radiographic progression (scale 0 to 448) was statistically significantly reduced in those on biologics + MTX/DMARDs versus comparator, MD -2.61 (95% CI -4.08 to -1.14). The absolute reduction was small, -0.58% (95% CI -0.91% to -0.25%) and we are unsure of the clinical relevance of this reduction. • NMA estimates of TNF biologic+MTX/DMARD (absolute reduction -0.67% (95% CrI -1.4% to -0.12%) and non-TNF biologic+MTX/DMARD (absolute reduction, -0.68% (95% CrI -2.36% to 0.92%)) were similar to respective direct estimates. • Direct evidence (moderate quality → downgraded for imprecision): results for withdrawals due to adverse events were inconclusive, with wide confidence intervals encompassing the null effect and evidence of an important increase in withdrawals, RR 1.11 (95% CI 0.96 to 1.30). • NMA estimates of TNF biologic+MTX/DMARD (RR 1.24 (95% CrI 0.99 to 1.57)) and non-TNF biologic+MTX/DMARD (RR 1.20 (95% CrI 0.87 to 1.67)) were similarly inconclusive and downgraded to low for both imprecision and indirectness. • Direct evidence of high quality: biologic+MTX/DMARD was associated with clinically significantly increased risk (statistically borderline significant) of serious adverse events on biologic+MTX/DMARD (Peto OR [can be interpreted as RR due to low event rate] 1.12 (95% CI 0.99 to 1.27); absolute risk 1% (0% to 2%). • NMA estimate for TNF biologic+MTX/DMARD (Peto OR 1.20 (95% CrI 1.01 to 1.43)) showed moderate quality evidence of an increase in the risk of serious adverse events. The other two NMA estimates were downgraded to low quality due to imprecision and indirectness and had wide confidence intervals resulting in uncertainty around the estimates: non-TNF biologics + MTX/DMARD: 1.07 (95% CrI 0.89 to 1.29) and anakinra: RR 1.06 (95% CrI 0.65 to 1.75). • Direct evidence (moderate quality → downgraded for serious imprecision: results were inconclusive for cancer (Peto OR 1.07 (95% CI 0.68 to 1.68) for all biologic+MTX/DMARD combinations. • NMA estimates of TNF biologic+MTX/DMARD (Peto OR 1.21 (95% CrI 0.63 to 2.38) and non-TNF biologic+MTX/DMARD (Peto OR 0.99 (95% CrI 0.58 to 1.78)) were similarly inconclusive and downgraded to low quality for both imprecision and indirectness. **Primärer Endpunkt→ Subgroup analyses by disease duration (early vs. established vs. late RA)** **Early RA (RA disease duration less than two years)** There were not enough data to perform NMA. **Established RA (disease duration two to 10 years)** Sixty trials with 24,984 participants (Appendix 5): compared to PL, all biologic and tofacitinib comparators in standard-dose and high-dose, with concomitant

	MTX, were associated with higher odds of ACR50, ranging from 3.01 to 20.7. Compared to MTX, most biologics + MTX, were associated with higher odds of ACR50, ranging from 2.12 to 6.93. Compared to DMARD, most biologics + DMARD, were associated with higher odds of ACR50, ranging from 3.2 to 24.5. Compared to MTX + DMARD, most standard-dose and high-dose biologics + MTX were associated with higher odds of ACR50, ranging from 2.2 to 5.1. Compared to standard-dose biologic, standard-dose biologic + MTX or high-dose biologic + MTX, were associated with higher odds of ACR50 in the 2 to 6-fold range. Biologic + DMARD was associated with lower odds of ACR50 compared to biologic + MTX, ranging from 0.13 to 0.31. In general, high-dose biologics + MTX were associated with higher odds of ACR50 compared to standard-dose + MTX. **Late RA (disease duration more than 10 years)** Twelve trials with 3481 participants (Appendix 6): compared to PL + MTX, standard-dose biologic + MTX and high-dose biologic + MTX were associated with higher odds of ACR50, in most cases. Compared to low-dose biologic, low-dose biologic + MTX was associated with higher odds of ACR50, ranging from 4.5 to 5.9.
	4. Fazit der Autoren: *Based primarily on RCTs of 6 months' to 12 months' duration, there is moderate quality evidence that the use of biologic+MTX/ DMARD in people with rheumatoid arthritis who have failed to respond to MTX or other DMARDs results in clinically important improvement in function and higher ACR50 and remission rates, and increased risk of serious adverse events than the comparator (MTX/DMARD/PL; high quality evidence). Radiographic progression is slowed but its clinical relevance is uncertain. Results were inconclusive for whether biologics + MTX/DMARDs are associated with an increased risk of cancer or withdrawals due to adverse events.*

Systematische Reviews

Hazlewood GS et al., 2016 [17]. Methotrexate monotherapy and methotrexate combination therapy with traditional and biologic disease modifying	**1. Fragestellung** To compare methotrexate based disease modifying antirheumatic drug (DMARD) treatments for rheumatoid arthritis in patients naive to or with an inadequate response to methotrexate.
	2. Methodik Systematic review and Bayesian random effects network meta-analysis Population: Adult patients with rheumatoid arthritis. Intervention / Komparator: methotrexate used alone or in combination with other conventional synthetic DMARDs, biologic drugs, or tofacitinib

antirheumatic drugs for rheumatoid arthritis: abridged Cochrane systematic review and network meta-analysis	Endpunkt: ACR 50 response (major clinical improvement), radiographic progression, and withdrawals due to adverse events Suchzeitraum (Aktualität der Recherche): bis Januar 2016 Anzahl eingeschlossene Studien/Patienten (Gesamt): 158 trials were included, with between 10 and 53 trials available for each outcome Qualitätsbewertung der Studien: Cochrane risk of bias & GRADE

3. Ergebnisdarstellung

Qualität der Studien: The risk of bias of the trials varied considerably across each domain (fig 3). The overall risk of bias was high in 30% of trials for ACR50 response, in 21% for radiographic progression, and in 17% for withdrawals due to adverse events. These trials were excluded from the primary analysis.

Methotrexate naive patients (siehe Tabelle 2):

- Several treatments were statistically superior to oral methotrexate for ACR50 response: sulfasalazine and hydroxychloroquine ("triple therapy"), several biologics (abatacept, adalimumab, etanercept, infliximab, rituximab, tocilizumab), and tofacitinib.
- The estimated probability of ACR50 response was similar between these treatments (range 56-67%), compared with 41% with methotrexate.
- Methotrexate combined with adalimumab, etanercept, certolizumab, or infliximab was statistically superior to oral methotrexate for inhibiting radiographic progression, but the estimated mean change over one year with all treatments was less than the minimal clinically important difference of 5 units on the Sharp-van der Heijde scale.
- Triple therapy had statistically fewer withdrawals due to adverse events than methotrexate plus infliximab.

Table 2 | Summary of findings: methotrexate naive patients

Intervention	Absolute risk (95% CrI)	Average treatment effect relative to oral MTX (95% CrI)	Probability treatment superior to oral MTX	No of trials providing direct evidence
Withdrawals due to adverse events (37 studies; 10528 patient years)	No of events/1000 patients in 1 year	Rate ratio	%	
MTX	76	Reference	–	–
MTX + abatacept (IV)	52 (15 to 163)	0.70 (0.21 to 2.35)	74	1
MTX + abatacept (SC)	71 (15 to 310)	0.97 (0.20 to 4.89)	52	1
MTX + adalimumab	88 (46 to 153)	1.21 (0.63 to 2.18)	24	4
IM/SC MTX + adalimumab	60 (5.1 to 458)	0.81 (0.07 to 8.06)	58	0
MTX + etanercept	59 (33 to 117)	0.80 (0.45 to 1.64)	77	3
MTX + golimumab (SC)	164 (49 to 520)	2.36 (0.67 to 9.67)	8	1
MTX + infliximab	175 (69 to 448)	2.53 (0.94 to 7.81)	3	4
MTX + rituximab	61 (17 to 204)	0.83 (0.22 to 3.01)	62	1
MTX + tocilizumab (4 mg/kg)	96 (35 to 249)	1.33 (0.46 to 3.77)	25	1
MTX + tocilizumab (8 mg/kg)	158 (61 to 384)	2.26 (0.82 to 6.38)	5	1
MTX + tofacitinib	66 (13 to 293)	0.90 (0.17 to 4.56)	55	1
MTX + azathioprine	356 (113 to 842)	5.79 (1.58 to 24.31)	1	3
MTX + ciclosporin	77 (28 to 166)	1.06 (0.37 to 2.38)	44	2
IM/SC MTX + ciclosporin	491 (71 to 999)	8.89 (0.98 to 139.30)	3	0
MTX + hydroxychloroquine/chloroquine	98 (30 to 392)	1.35 (0.40 to 5.26)	30	1
MTX + sulfasalazine	95 (49 to 190)	1.31 (0.67 to 2.78)	21	4
MTX + sulfasalazine + hydroxychloroquine	49 (21 to 109)	0.67 (0.28 to 1.51)	84	2
IM/SC MTX	131 (42 to 399)	1.85 (0.56 to 6.69)	14	1

Methotrexate-experienced patients (siehe Tabelle 3):

	• After an inadequate response to methotrexate, several treatments were statistically superior to oral methotrexate for ACR50 response: triple therapy, methotrexate plus hydroxychloroquine, methotrexate plus leflunomide, methotrexate plus intramuscular gold, methotrexate plus most biologics, and methotrexate plus tofacitinib. • The probability of response was 61% with triple therapy and ranged widely (27-70%) with other treatments. • No treatment was statistically superior to oral methotrexate for inhibiting radiographic progression. • Methotrexate plus abatacept had a statistically lower rate of withdrawals due to adverse events than several treatments.

Table 3 | Summary of findings: methotrexate inadequate response patients

Intervention	Absolute risk (95% CrI)	Average treatment effect relative to oral MTX (95% CrI)	Probability treatment superior to oral MTX	No of trials providing direct evidence
ACR50 (45 studies; 12549 patients)	**No of events/1000 patients at 1 year**	**Odds ratio**	**%**	
MTX	127	Reference	–	–
MTX + abatacept (IV)	357 (290 to 437)	3.81 (2.80 to 5.33)	>99	5
MTX + abatacept (SC)	377 (284 to 488)	4.16 (2.72 to 6.53)	>99	0
MTX + adalimumab	389 (330 to 462)	4.37 (3.38 to 5.89)	>99	10
MTX + etanercept	642 (456 to 818)	12.31 (5.76 to 30.78)	>99	3
MTX + golimumab (SC)	395 (273 to 539)	4.49 (2.57 to 8.01)	>99	3
MTX + golimumab (IV)	343 (207 to 514)	3.58 (1.79 to 7.25)	>99	1
MTX + infliximab	335 (264 to 422)	3.46 (2.46 to 5.00)	>99	6
MTX + rituximab	343 (241 to 477)	3.59 (2.18 to 6.27)	>99	3
MTX + tocilizumab (4 mg/kg)	273 (171 to 399)	2.57 (1.42 to 4.56)	>99	2
MTX + tocilizumab (8 mg/kg)	377 (264 to 499)	4.16 (2.46 to 6.85)	>99	3
MTX + tofacitinib	441 (325 to 568)	5.42 (3.31 to 9.01)	>99	3
MTX + hydroxychloroquine/chloroquine	566 (241 to 871)	8.94 (2.18 to 46.14)	>99	0
MTX + IM gold	704 (228 to 988)	16.34 (2.03 to 553.42)	>99	1
MTX + leflunomide	453 (245 to 703)	5.69 (2.23 to 16.27)	>99	1
MTX + sulfasalazine	267 (67 to 667)	2.50 (0.49 to 13.76)	87	0
MTX + sulfasalazine + hydroxychloroquine	605 (394 to 818)	10.51 (4.46 to 30.81)	>99	0
Radiographic progression (10 studies; 3238 patients)	**Mean change on Sharp-VdH scale over 1 year (points)**	**Standardized mean difference**	**%**	
MTX	3.35	Reference	–	–
MTX + abatacept (IV)	1.45 (–5.85 to 8.80)	–0.30 (–1.44 to 0.85)	84	1
MTX + abatacept (SC)	0.26 (–9.65 to 11.10)	–0.48 (–2.03 to 1.21)	86	0
MTX + adalimumab	0.51 (–6.42 to 7.96)	–0.44 (–1.53 to 0.72)	90	1
MTX + etanercept	–0.49 (–12.09 to 11.06)	–0.60 (–2.41 to 1.21)	87	0
MTX + golimumab (SC)	2.44 (–2.77 to 7.66)	–0.14 (–0.96 to 0.67)	76	2
MTX + golimumab (IV)	0.52 (–6.56 to 7.98)	–0.44 (–1.55 to 0.73)	89	1
MTX + infliximab	–1.08 (–8.34 to 6.35)	–0.69 (–1.83 to 0.47)	94	1
MTX + sulfasalazine + hydroxychloroquine	0.70 (–9.58 to 11.05)	–0.41 (–2.02 to 1.20)	82	0
Withdrawals due to adverse events (53 studies; 9950 patient years)	**No of events/1000 patients in 1 year**	**Rate ratio**	**%**	
MTX	73	Reference	–	–
MTX + abatacept (IV)	54 (31 to 90)	0.76 (0.44 to 1.30)	85	6
MTX + abatacept (SC)	39 (21 to 72)	0.55 (0.28 to 1.03)	97	0
MTX + adalimumab	100 (67 to 155)	1.44 (0.95 to 2.30)	4	8
MTX + certolizumab	99 (56 to 196)	1.42 (0.79 to 2.99)	13	4
MTX + etanercept	89 (40 to 195)	1.28 (0.56 to 2.92)	29	3
MTX + golimumab (SC)	72 (28 to 184)	1.02 (0.39 to 2.78)	48	3
MTX + golimumab (IV)	92 (26 to 370)	1.32 (0.36 to 6.31)	34	1
MTX + infliximab	112 (70 to 179)	1.62 (0.99 to 2.70)	3	6
MTX + rituximab	141 (53 to 376)	2.07 (0.74 to 6.45)	8	3
MTX + tocilizumab (4 mg/kg)	112 (67 to 191)	1.63 (0.95 to 2.90)	4	3
MTX + tocilizumab (8 mg/kg)	118 (74 to 188)	1.71 (1.01 to 2.84)	2	5
MTX + tofacitinib	87 (52 to 152)	1.24 (0.74 to 2.26)	21	4
MTX + ciclosporin	212 (84 to 503)	3.27 (1.20 to 9.57)	1	2
MTX + IM gold	260 (35 to 999)	4.12 (0.49 to 102.75)	10	1
MTX + leflunomide	127 (53 to 290)	1.86 (0.74 to 4.68)	8	1
MTX + sulfasalazine + hydroxychloroquine	125 (62 to 249)	1.82 (0.87 to 3.92)	5	0

	4. Fazit der Autoren: *Triple therapy (methotrexate plus sulfasalazine plus hydroxychloroquine) and most regimens combining biologic DMARDs with methotrexate were effective in controlling disease activity, and all were generally well tolerated in both methotrexate naive and methotrexate exposed patients.*
Canadian Agency for Drugs and Technologies	1. Fragestellung 1. What is the clinical effectiveness and safety of switching biologics for adult patients with rheumatoid arthritis (RA)?

in Health, 2015 [5]. Biologic Switching for Patients with Rheumatoid Arthritis: A Review of Clinical Effectiveness, Safety, and Guidelines	2. What are the evidence-based guidelines associated with switching biologics for adult patients with RA?
	2. Methodik Population: Adult patients with RA Intervention: Biologics: TNF-α inhibitors (i.e., adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab); β-cell depletors (i.e., rituximab); Interleukin-1 inhibitors (i.e., anakinra); Interleukin-6 inhibitors (i.e., tocilizumab); Janus kinase inhibitors (i.e., tofacitinib); T-cell co-stimulation inhibitors (i.e., abatacept) Komparator: Biologics (i.e., switching within class and switching out of class) Endpunkt: siehe Ergebnisteil Suchzeitraum (Aktualität der Recherche): January 1, 2010 and November 10, 2015 Anzahl eingeschlossene Studien/Patienten (Gesamt): 17 publications met the inclusion criteria and were included in this report.The 17 publications comprised five SRs two RCTs and eight evidence-based guidelines (with relevant details reported in ten publications). Specifically, two guidelines by the American College of Rheumatology (ACR) and Brazilian Society of Rheumatology American College of Rheumatology (BSR) are represented by two publications each. *Hinweis*: Es wurden folgende Studiendesigns eingeschlossen: Health technology assessments (HTAs), SRs, meta-analyses (MAs), RCTs, and evidence-based guidelines Qualitätsbewertung der Studien: The included SRs, RCTs, and evidence-based guidelines were critically appraised, using the Assessment of Multiple Systematic Reviews (AMSTAR) tool, Downs and Black instrument, and the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument, respectively. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included study were described.
	3. Ergebnisdarstellung *Hinweis*: *Patient Population* → Five SRs included adult patients with RA who previously had an inadequate response or an exposure to one or more TNF-α inhibitors. Two RCTs included adult patients with RA who had discontinued one or more TNF-α inhibitors for lack of efficacy, intolerance, or other reasons (e.g., cost or insurance coverage issues). *Interventions and Comparators* → Five SRs compared switching from one or more TNF-α inhibitors to another biologic, whether a TNF-α inhibitor (i.e., within-class) or non-TNF biologic (i.e., out-of-class), versus switching to placebo, no other treatment, or another biologic. Two SRs made indirect pairwise comparisons between biologics, using the results of placebo-controlled trials, considering the lack of head-to-head trials. All intervention and control groups were administered with concurrent synthetic DMARDs. Two RCTs compared switching from one or more TNF-α inhibitors to another TNF-α inhibitor (i.e., within-class), specifically certolizumab pegol or golimumab, versus switching to placebo. All intervention and control

groups were administered with concurrent synthetic DMARDs.

Qualität der Studien und Systematischen reviews:
Five SR were of variable quality. Duplicate study selection and data extraction was conducted in three SRs. A comprehensive literature search was conducted in three SRs including grey literature, whereas no detailed search strategy was provided in two SRs. Four SRs provided a list of the included studies and their characteristics, but only one SR provided a list of the excluded studies. The scientific quality of the included studies was assessed in all five SRs but not explicitly described in two SRsand not used in formulating conclusions in one SR. None of the five SRs assessed the likelihood of publication bias. While two SRs declared no conflict of interest, one SR made no statement, and two SRs declared previous involvement with pharmaceutical companies and technology assessments.
Two RCTs were generally of poor quality.

What is the clinical effectiveness and safety of switching biologics for adult patients with RA?

ACR 20/50/70 Responses:
Five SRs and two RCTs reported that switching from one or more TNF-α inhibitors to another biologic, whether a TNF-α inhibitor (i.e., certolizumab pegol, golimumab, or unspecified TNF-α inhibitors as a class) or non-TNF inhibitor (i.e., abatacept, rituximab, or tocilizumab), provided significant improvement in treatment response over placebo or no other treatment, when taken in combinations with synthetic DMARDs. For example, the odd ratios (ORs), with the 95% confidence intervals (CIs), of achieving the ACR 20 response at 24 weeks, comparing biologics to placebo, fell in the following ranges, presented as the OR (95% CI):

- Between 2.577 (1.518 to 4.496)7 and 3.325 (1.71 to 6.47)11 for golimumab
- Between 4.180 (2.55 to 6.85)11 and 4.226 (2.606 to 7.023)7 for abatacept
- Between 4.736 (3.10 to 7.25)11 and 4.822 (3.176 to 7.492)7 for rituximab
- Between 8.901 (4.86 to 16.31)11 and 9.060 (5.064 to 17.000)7 for tocilizumab

Using indirect pairwise comparisons, two SRs reported greater improvement in treatment response with switching to tocilizumab compared to another TNF-α inhibitor (i.e., golimumab), but only one SR demonstrated statistically significant differences with switching to abatacept or rituximab compared to golimumab

HAQ-DI Scores
Four SRs and two RCTs reported that switching from one or more TNF-α inhibitors to another biologic, whether a TNF-α inhibitor (i.e., certolizumab pegol, golimumab, or unspecified TNF-α inhibitors as a class) or non-TNF inhibitor (i.e., abatacept, rituximab, or tocilizumab), provided significant improvement in physical function over placebo or no other treatment, when taken in combinations with synthetic DMARDs. For example, the mean differences (MDs), with the 95% CIs, in reductions in the HAQ-DI scores at 24 weeks, comparing biologics to placebo, were as follows, presented as the MD (95% CI):

- -0.140 (-0.255 to -0.026)7 for golimumab
- -0.400 (-0.499 to -0.299)7 for abatacept
- -0.300 (-0.397 to -0.203)7 for rituximab
- -0.340 (-0.453 to -0.227)7 for tocilizumab

Using indirect pairwise comparisons, one SR7 reported greater improvement in physical function with switching to non-TNF biologics (i.e., abatacept, rituximab, or tocilizumab), compared to another TNF-α inhibitor (i.e., golimumab). For example, the MDs, with the 95% CIs, in reductions in the HAQ-DI scores at 24 weeks, comparing biologics to golimumab, were

	as follows, presented as the MD (95% CI): • -0.260 (-0.411 to -0.107)7 for abatacept • -0.160 (-0.310 to -0.010)7 for rituximab • -0.200 (-0.360 to -0.039)7 for tocilizumab **Disease Activity and DAS 28 and CDAI Scores** Two SRs and two RCTs reported that switching from one or more TNF-α inhibitors to another biologic, whether a TNF-α inhibitor (i.e., certolizumab pegol or golimumab) or non-TNF inhibitor (i.e., abatacept, rituximab, or tocilizumab), provided significant improvement in disease activity over placebo or no other treatment, when taken in combinations with synthetic DMARDs. For example, the risk ratio (RR) for achieving low disease activity for switching to abatacept, rituximab, or tocilizumab, compared to the control at six months, after TNF-α inhibitor failure, was 6.59, with the 95% CI 4.01 to 10.82. The RR for the DAS 28 remission for tocilizumab was 10.02, with the 95% CI 3.20 to 31.42.14 The CDAI low disease activity (i.e., CDAI < 10) was significantly higher in the patients treated with certolizumab pegol after 12 weeks, compared to the patients treated with placebo (no effect sizes were provided, with a *p*-value = 0.046). **EULAR Response** One SR12 reported that switching from one or more TNF-α inhibitors to a non-TNF inhibitor (i.e., rituximab) provided significant improvement in patient response over placebo or no other treatment, when taken in combinations with synthetic DMARDs. The RR for achieving the good or moderate EULAR response was 2.96, with the 95% CI 2.25 to 3.89. **SF-36 Scores** One SR reported that that switching from one or more TNF-α inhibitors to a non-TNF inhibitor (i.e., abatacept or rituximab), provided significant improvement in quality of life over placebo or no other treatment, when taken in combinations with synthetic DMARDs. The MD between the intervention and control groups in the SF-36 mental and health scores, respectively, was 3.70, with the 95% CI 1.45 to 5.95, and 5.50, with the 95% CI 3.74 to 7.26, for abatacept and 3.07 and 5.16, with the 95% CI not reported, for rituximab. **Incidences of Adverse Events, Infections, and Injection Site or Infusion Reactions** Two SRs and two RCTs reported that the risk of adverse events or infections associated with switching from one or more TNF-α inhibitors to another biologic, whether a TNF-α inhibitor (i.e., certolizumab pegol, golimumab, or unspecified TNF-α inhibitors as a class) or non-TNF inhibitor (i.e., abatacept, rituximab, or tocilizumab), was comparable to placebo or no other treatment, when taken in combinations with synthetic DMARDs. One SR reported no differences in the risk of injection site reactions or infusion reactions for abatacept or rituximab versus placebo. Using indirect pairwise comparisons, one SR reported significantly fewer adverse events for switching to golimumab compared to abatacept, rituximab, or tocilizumab. The risk differences (RD), comparing biologics to golimumab, were 0.13 for abatacept, 0.18 for rituximab, and 0.18 for tocilizumab, with the 95% CI not reported.
	4. Fazit der Autoren: *The majority of studies focused on adult patients with RA who had an inadequate response or were intolerant to one or more TNF-α inhibitor. Five SRs and two RCTs reported significant improvement in various measures of clinical effectiveness (i.e., treatment response, physical function, joint damage, disease activity, quality of life, or treatment withdrawals), without significant increase in safety issues (i.e., adverse events, infections, or injection site or infusion reactions),*

	associated with switching from one or more TNF-α inhibitors to another biologic, whether a TNF-α inhibitor (i.e., certolizumab pegol, golimumab, or unspecified TNF-α inhibitors as a class) or non-TNF inhibitor (i.e., abatacept, rituximab, or tocilizumab), over placebo or no other treatment. Two SRs reported greater improvement with switching to the non-TNF biologic tocilizumab (i.e., out-of-class switching), compared to another TNF-α inhibitor, golimumab (i.e., within-class switching), while only one SR reported statistically significant greater improvement with switching to the non-TNF biologics abatacept or rituximab compared to golimumab. One RCT reported greater improvement in treatment response with switching to golimumab from etanercept or infliximab, compared to from adalimumab, and also from one previous TNF-α inhibitor, compared to two or three previous TNF-α inhibitors. All intervention and control groups were administered with concurrent synthetic DMARDs. The five SRs were of variable quality, and two RCTs were of poor quality. Therefore, the evidence presented in this report should be interpreted with caution. 5. Hinweise durch FB Med • The SRs included in this report identified a limited number of relevant studies, ranging from three to seven primary studies, none of which were head-to-head RCTs directly comparing one biologic to another biologic (instead of placebo or no treatment)
Lee YH et al., 2015 [22]. Comparative efficacy and safety of tocilizumab, rituximab, abatacept and tofacitinib in patients with active rheumatoid arthritis that inadequately responds to tumor necrosis factor inhibitors: a Bayesian network meta-analysis of	1. Fragestellung This study aimed to assess the relative efficacy and safety of biologics and tofacitinib in patients with rheumatoid arthritis (RA) showing an inadequate response to tumor necrosis factor (TNF) inhibitors
	2. Methodik Bayesian network meta-analysis Population: RA patients with active disease that failed to respond to TNF inhibitors and were started on a second line biologic drug Intervention / Komparator: tocilizumab, rituximab, abatacept and tofacitinib Endpunkt: ACR20 (primärer Endpunkt), ACR50, ACR70,response rates, and remission Suchzeitraum (Aktualität der Recherche): up to March 2015 Anzahl eingeschlossene Studien/Patienten (Gesamt): Four RCTs including 1796 patients met the inclusion criteria Qualitätsbewertung der Studien: The Jadad scale. Quality was classified as high (score of 3–5) versus low (score of 0–2).

randomized controlled trials	3. Ergebnisdarstellung Qualität der Studien: Jadad scores of the studies were 3–4, indicating high study quality *Hinweis*: Inconsistency and sensitivity analysis Inconsistency plots that assessed network inconsistencies between direct and indirect estimates showed no evidence those inconsistencies may significantly affect the network meta-analysis results. • The tocilizumab 8 mg group showed a significantly higher American College of Rheumatology 20% (ACR20) response rate than the abatacept and tofacitinib groups. • Ranking probability based on surface under the cumulative ranking curve (SUCRA) indicated that tocilizumab 8 mg had the highest probability of being the best treatment for achieving the ACR20 response rate (SUCRA = 0.9863), followed by rituximab (SUCRA = 0.6623), abatacept (SUCRA = 0.5428), tocilizumab 4 mg (SUCRA = 0.4956), tofacitinib 10 mg (SUCRA = 0.4715), tofacitinib 5 mg (SUCRA = 0.3415) and placebo (SUCRA = 0). • In contrast, the safety based on the number of withdrawals due to adverse events did not differ significantly among the treatment options.
	4. Fazit der Autoren: *In conclusion, using a Bayesian network meta-analysis involving 1796 patients, we found that tocilizumab 8 mg was the second-line non-TNF biologic with the highest performance regarding an early good response based on ACR20 response and acceptable safety profile, followed by rituximab, abatacept and tofacitinib, and none of these options was associated with a significant risk of withdrawal due to AEs. Our results suggest a difference in efficacy among biologics and tofacitinib in patients with active RA refractory to anti-TNF therapy. Long-term studies are needed to determine the relative efficacy and safety of biologics and tofacitinib in a large number of patients with active RA that inadequately responds to TNF inhibitors.* 5. Hinweise durch FB Med • Es sind die allgemeinen Limiationen bei indirekten Vergleichen zu beachten
Stevenson M et al., 2016 [46]. Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept	1. Fragestellung The objective was to assess the clinical effectiveness and cost-effectiveness of seven biologic disease-modifying antirheumatic drugs (bDMARDs) compared with each other and conventional disease-modifying antirheumatic drugs (cDMARDs). The decision problem was divided into those patients who were cDMARD naive and those who were cDMARD experienced; whether a patient had severe or moderate to severe disease; and whether or not an individual could tolerate methotrexate (MTX).
	2. Methodik A systematic review of randomised controlled trials of efficacy was undertaken. Network meta-analyses (NMAs) were undertaken for patients who were cDMARD

for the treatment of rheumatoid arthritis not previously treated with disease-modifying antirheumatic drugs and after the failure of conventional disease-modifying antirheumatic drugs only: systematic review and economic evaluation	naive and for those who were cDMARD experienced. Sensitivity analyses were undertaken to explore the impact of including RCTs with a small proportion of bDMARD experienced patients and where MTX exposure was deemed insufficient → NMAs were conducted to determine efficacy using two different disease activity measures (ACR and EULAR responses) Population: The three populations under consideration in this assessment were: i. Adults with severe active RA not previously treated with MTX (defined by a DAS of ≥ 5.1). In the original protocol29 this population was defined as 'adults with severe active RA not previously treated with MTX or other DMARDs (defined by a DAS of ≥ 5.1)'. However, this definition was subsequently modified and broadened by the Assessment Group (in consultation with clinical experts) to include 'adults with severe active RA not previously treated with MTX' to permit the inclusion of trial populations relevant to the decision problem which were MTX naive, but may have had some prior experience of other cDMARDs. ii. Adults with severe active RA who had been previously treated with conventional DMARDs only, including MTX (unless contraindicated or inappropriate) (defined by a DAS of ≥ 5.1). iii. Adults with moderate to severe active RA who had been previously treated with conventional DMARDs only, including MTX (unless contraindicated or inappropriate) (defined as a DAS between 3.2 and 5.1). Intervention: The following interventions were included: 1. For RA not previously treated with MTX: i. ADA ii. ETN iii. IFX iv. GOL. 2. For RA that has been previously treated with conventional DMARDs only: i. ADA ii. ETN iii. IFX iv. CTZ v. GOL vi. ABT (i.v. and s.c. preparations) vii. TCZ. The above interventions were assessed in accordance with licensed indications and could be delivered in conjunction with cDMARDs or as monotherapy (as defined in licensed indications). Komparator: The relevant comparators differed according to the population considered and included the following: 1. For severe active RA not previously treated with MTX: iv. combination therapy with conventional DMARDs (including MTX and at least one other DMARD, such as SSZ and LEF) or DMARD monotherapy with dose escalation v. biologic interventions compared with each other. 2. For severe active RA that has been previously treated with conventional DMARDs

	only: i. management strategies involving further conventional DMARDs (e.g. SSZ, LEF), NSAIDs and corticosteroids ii. biologic interventions compared with each other. 3. For moderate to severe active RA that has been previously treated with conventional DMARDs only: i. management strategies involving further conventional DMARDs (e.g. SSZ, LEF), NSAIDs and corticosteroids ii. biologic interventions compared with each other. Endpunkte: disease activity (DAS28, ACR and EULAR responses, swollen and tender joint counts and patient and physician global assessments of disease activity); physical function [Health Assessment Questionnaire Disability Index (HAQ-DI), but not modified versions of HAQ]; joint damage/radiological progression; pain; mortality; fatigue; extra-articular manifestations of disease; health-related quality of life l adverse effects of treatment Suchzeitraum (Aktualität der Recherche): Systematische Literaturrecherche bis 2013 Anzahl eingeschlossene Studien/Patienten (Gesamt): Of the remaining records, a total of 60 studies were included in the review. Sixty RCTs were included in the systematic review of clinical effectiveness. These comprised six trials with head-to-head comparisons of included biologic interventions, [academic-in-confidence (AiC) information has been removed, and 53 trials of biologic interventions compared with placebo (PBO) or cDMARDs. Methotrexate-naive trial populations are considered separately in the following results section as population 1. For population 1 there were a total of 15 RCTs included in the systematic review (ABT n = 0, ADA n = 6,CTZ n=0, ETN n=2, GOL n=1, IFX n=5, TCZ n=0 and head-to-head biologics n=1). Eight of the MTX-naive trials had data available for the NMA. All these seven trials provided ACR data; however, only one90 contributed EULAR data for analysis. A head-to-head trial of ADA versus ETN was identified but this trial was not eligible for the NMA (due to early escape at 12 weeks with no imputation for missing data). There were 45 trials with cDMARD-experienced populations (considered as populations 2 and 3) (ABT n=3, ADA n=7, CTZ n=2, ETN n=11, GOL n=3, IFX n=7, TCZ n=6, head-to-head biologics n=5 and grouped antiTNFs n = 1). Of these, 30 trials had data available for the NMA. Qualitätsbewertung der Studien: The quality assessment of included studies was informed by selected items listed in the NHS Centre for Reviews and Dissemination report48 and Cochrane Risk of Bias tool
	3. Ergebnisdarstellung <u>Qualität der Studien</u>: Generally, risk of bias was low overall, and low for baseline comparability, blinding, analysis by allocated treatment group and inclusion of ≥ 80% of

	participants randomised in the final analysis. There was greater risk of bias and a lack of clarity in many included trials for allocation sequence generation and concealment, and selective reporting of outcomes. Population 1: Although there was uncertainty in, and overlap between, the effects of treatment on ACR for interventions for patients in population 1, IFX plus MTX was associated with the biggest increase in response rate and this was likely to be the most effective intervention. Other interventions were less effective and appeared to fall into three groups: (1) intensive cDMARDs and ADA plus MTX; (2) ETN, GOL plus MTX and step-up combination cDMARDs; and (3) ADA and cDMARDs. Population 2: Although there was uncertainty in, and overlap between, the effects of treatment on EULAR for interventions in populations 2 and 3 in the main trials, ETN plus MTX and TCZ plus MTX were associated with the biggest increase in response rate. Other interventions were less effective and appeared to fall into two groups: (1) TCZ, GOL plus MTX, ADA plus MTX, ABT intravenous (i.v.) plus MTX and grouped biologics; and (2) ETN, IFX plus MTX, ADA and intensive cDMARDs. The inclusion of the additional studies in which patients received prior biologics resulted in broadly the same groupings, although CTZ plus MTX was associated with an even bigger response than ETN plus MTX and TCZ plus MTX. Population 2 and 3: Although there was uncertainty in, and overlap between, the effects of treatment on ACR for interventions in populations 2 and 3 in the main trials, ETN plus MTX, TCZ and TCZ plus MTX were associated with the biggest increase in response rate. Other interventions were less effective and appeared to fall into two groups: (1) ETN, GOL plus MTX, ABT subcutaneous plus MTX, ADA plus MTX, IFX plus MTX and ABT i.v. plus MTX; and (2) CTZ plus MTX, intensive cDMARDs and ADA. The inclusion of the additional studies in which patients received prior biologics suggested that CTZ plus MTX and ETN plus MTX resulted in the highest response rates. Other interventions appeared to give rise to broadly similar and slightly smaller response rates except for intensive cDMARDs and ADA which are associated with even smaller response rates.
	4. Fazit der Autoren: *Key research priorities include establishing, more precisely, HAQ progression while on cDMARDs; the relationship between HAQ score and utility; and the relationship between HAQ score and pain. Better evidence on the relative efficacies of bDMARDs and the reduction in efficacy when used after a different bDMARD would be beneficial, but it is acknowledged that large RCTs would be required to provide definitive answers.*
Donahue KE, 2012 [10]. Drug Therapy for Rheumatoid Arthritis in Adults: An Update.	**1. Fragestellung** Compare the benefits and harms of corticosteroids, oral and biologic diseasemodifying antirheumatic drugs (DMARDs) for adults with RA. Key Questions (KQs): • KQ1: For patients with RA, do drug therapies differ in their ability to reduce disease activity, to slow or limit the progression of radiographic joint damage, or to maintain remission? • KQ2: For patients with RA, do drug therapies differ in their ability to improve patient reported symptoms, functional capacity, or quality of life? • KQ3: For patients with RA, do drug therapies differ in harms, tolerability, patient adherence, or adverse effects? • KQ4: What are the comparative benefits and harms of drug therapies for RA in subgroups of patients based on stage of disease, prior therapy, demographics,

	concomitant therapies, or comorbidities?
	2. Methodik ***Population:*** Patienten mit RA ***Intervention:*** Corticosteroids, oral DMARDs, and biologic DMARDs ***Kontrolle(n):*** Corticosteroids, oral DMARDs, and biologic DMARDs, placebo ***Endpunkte:*** <u>Efficacy/effectivness</u> • KQ 1: - Disease activity - Radiographic joint damage - Remission • KQ 2: - Functional capacity - Quality of life - Patient-reported symptoms • KQ 3: Harms, tolerability, adherence, adverse effects • KQ 4: Benefits and harms in subgroups based on stage, history of prior therapy, demographics, concomitant therapies, comorbidities ***Suchzeitraum (Aktualität der Recherche):*** 1980 – 02/2011 Nur RCTs, Beobachtungsstudien mit mehr als 100 Patienten, systematische Reviews ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 31 head-to-head RCTs 1 head-to-head nicht-randomisiert/kontrollierte Studie 44 Placebo-kontrollierte Studien 28 Metaanalysen oder systematische Reviews 107 Observationsstudien identifiziert Included articles by key question KQ1 TOTAL = 125 (62) KQ2 TOTAL = 80 (47) KQ3 TOTAL = 201 (101) KQ4 TOTAL = 6 (2) *Some articles were included for more than one KQ, The first number listed includes all references identified in both the original and update reports ***Qualitätsbewertung der Studien:*** „To assess the internal validity of individual studies, the EPC adopted criteria for assessing the internal validity of individual studies from the U.S. Preventive Services Task Force and the NHS Centre for Reviews and Dissemination. To assess the quality of observational studies, we used criteria outlined by Deeks et al., 2003 (graded the strength of evidence for the outcomes determined).” Strength of Evidence: • ***High****:* Further research is very unlikely to change our confidence in the estimate of effect.

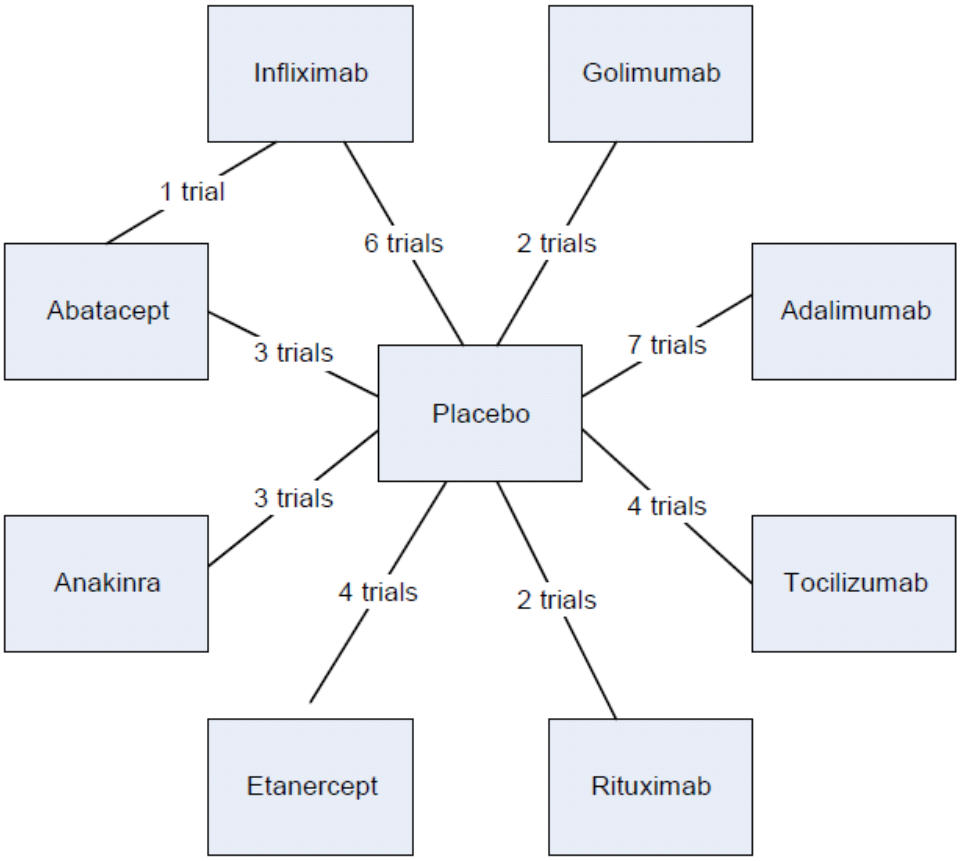
- ***Moderate**:* Further research may change our confidence in the estimate of effect and may change the estimate.
- ***Low**:* Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.
- ***Insufficient***: Evidence either is unavailable or does not permit estimation of an effect.

3. Ergebnisdarstellung

Evidenzbewertung:
Auswertung der Evidenz nach:

- individual oral DMARD vs. oral DMARD,
- oral DMARD combinations (with or without corticosteroids) vs. oral DMARD combinations,
- biologic vs. biologic, biologic vs. oral DMARD,
- biologics plus oral DMARD vs. biologic,
- biologic plus oral DMARD vs. oral DMARD,
- early RA strategies.
-

Figure 2. Evidence network for ACR 50 mixed treatment comparisons



Note: The total number of trials does not appear to equal30 (the total number of studies included in the analysis) because some trials have multiple arms that were included.

Direkter Vergleich: Adatacept vs. Infliximab: kein Unterschied nach 1 Jahr[1]:

- We found one head-to-head RCT that compared one biologic DMARD with

[1] Schiff M, Keiserman M, Codding C, et al. Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheu-matoid arthritis and an inadequate response to methotrexate. Ann Rheum Dis. 2008 Aug; 67(8):1096-103. PMID: 18055472.

another providing low strength of evidence that abatacept lessens disease activity at 1 year compared with infliximab. However, remission by DAS did not reach significance at 1 year.

Other existing direct head-to-head evidence is limited to a non-randomized, open-label effectiveness trial and six prospective cohort studies

Alle direkten und indirekten Vergleiche:

Table A. Summary of findings with strength of evidence

Key Comparisons	Efficacy Strength of Evidence	Harms Strength of Evidence
Oral DMARD vs. Oral DMARD		
Leflunomide vs. MTX	No differences in ACR 20 or radiographic responses. **Low** No clinically significant difference for functional capacity. **Low** Greater improvement in health-related quality of life (SF-36 physical component) for leflunomide. **Low**	No consistent differences in tolerability and discontinuation rates. **Low** Mixed results for specific adverse events. **Insufficient**
Leflunomide vs. sulfasalazine	Mixed ACR response rates. **Insufficient** No differences in radiographic changes. **Low** Greater improvement in functional capacity for leflunomide **Low**	No differences in tolerability and discontinuation rates. **Low** Mixed results for specific adverse events. **Insufficient**
Sulfasalazine vs. MTX	No differences in ACR 20 response, disease activity scores and radiographic changes.† **Moderate** No differences for functional capacity.† **Moderate**	No differences in tolerability; more patients stayed on MTX long term. **Low** Mixed results for specific adverse events. **Insufficient**
Oral DMARD Combinations vs. Oral DMARD		
Sulfasalazine plus MTX vs. sulfasalazine or MTX monotherapy	In patients with early RA, no differences in ACR 20 response rates or radiographic changes. **Moderate** No differences in functional capacity. **Moderate**	Withdrawal rates attributable to adverse events higher with combination. **Low** Insufficient evidence for specific adverse events. **Insufficient**

Table A. Summary of findings with strength of evidence (continued)

Key Comparisons	Efficacy Strength of Evidence	Harms Strength of Evidence
Oral DMARD plus prednisone vs. oral DMARD	Mixed results for disease activity. **Insufficient** Less radiographic progression in patients on DMARD plus prednisone. **Low** In patients with early RA, significantly lower radiographic progression and fewer eroded. joints **Low** Greater improvement in functional capacity for one oral DMARD plus prednisolone than for oral DMARD monotherapy. **Moderate** No difference in quality of life. **Low**	No differences in discontinuation rates; addition of corticosteroid may increase time to discontinuation of treatment. **Moderate** No differences in specific adverse events, except addition of corticosteroid may increase wound-healing complications. **Low**
Biologic DMARDs vs. Biologic DMARDs		
Abatacept vs. Infliximab	Greater improvement in disease activity for abatacept, but no difference in remission or functional capacity. Statistically significant difference between groups for quality of life (SF-36 PCS) that did not reach the minimal clinically important difference. **Low**	Discontinuation rates and severe adverse events higher with infliximab. **Low**
Biologic vs. biologic *(Mixed treatment comparisons)*	No significant differences in disease activity (ACR 50) in MTC analyses between abatacept, adalimumab, golimumab, infliximab, rituximab, and tocilizumab in patients resistant to MTX. **Low** Less improvement in disease activity (ACR 50) for anakinra compared with etanercept and compared with adalimumab in MTC analyses in patients resistant to MTX. Comparisons with abatacept, golimumab, infliximab, rituximab, and tocilizumab did not reach statistical significance. **Low**	Adjusted indirect comparisons found a more favorable withdrawal profile for certolizumab pegol than other biologic DMARDs. Also, etanercept and rituximab had a more favorable overall withdrawal profile than some other biologic DMARDs. Certolizumab pegol had fewer withdrawals due to lack of efficacy than adalimumab, anakinra, and infliximab. All but adalimumab, golimumab, and infliximab had fewer withdrawals than anakinra due to lack of efficacy. Both certolizumab pegol and infliximab had more withdrawals due to adverse events than etanercept and rituximab. **Low**
Biologic vs. biologic *(Mixed treatment comparisons)* (continued)	Greater improvement in disease activity (ACR 50) for etanercept compared with abatacept, adalimumab, anakinra, infliximab, rituximab, and tocilizumab in MTC analyses. No significant differences when compared with golimumab. **Low**	Risk for injection site reactions apparently highest with anakinra. **Low** Mixed results for specific adverse events. **Insufficient**
Biologic DMARDs vs. Oral DMARDs		
Anti-tumor necrosis factor drugs vs. MTX	In patients with early RA, no clinically significant differences in clinical response between adalimumab or etanercept and MTX; in patients on biologic DMARDs, better radiographic outcomes than in patients on oral DMARDs. **Moderate** No difference in functional capacity between adalimumab and MTX for MTX-naïve subjects with early RA; mixed results for etanercept vs. MTX. **Low**; **Insufficient** Faster improvement in quality of life with etanercept than MTX. **Low**	No differences in adverse events in efficacy studies. **Low** Insufficient evidence on differences in the risk for rare but severe adverse events. **Insufficient**

Key Comparisons	Efficacy Strength of Evidence	Harms Strength of Evidence
Biologic DMARD Combinations		
Biologic DMARD plus biologic DMARD vs. biologic DMARD	No additional benefit in disease activity or functional capacity from combination of etanercept plus anakinra compared with etanercept monotherapy or combination of etanercept plus abatacept compared with abatacept monotherapy, but greater improvement in quality of life with etanercept plus abatacept vs. etanercept. **Low**	Substantially higher rates of serious adverse events from combination of two biologic DMARDs than from monotherapy. **Moderate**

Key Comparisons	Efficacy Strength of Evidence	Harms Strength of Evidence
Biologic DMARDs plus MTX vs. biologic DMARDs	Better improvements in disease activity from combination therapy of biologic DMARDs (adalimumab, etanercept, infliximab, rituximab) plus MTX than from monotherapy with biologics. **Moderate** In MTX-naive patients with early aggressive RA, better ACR 50 response, significantly greater clinical remission, and less radiographic progression in the combination therapy group. **Low** In MTX-naïve subjects or those not recently on MTX, greater improvement in functional capacity (**Moderate**) and quality of life (**Low**) with combination therapy. In subjects with active RA despite treatment with MTX, no difference in functional capacity or quality of life. **Low**	No differences in adverse events in efficacy studies. **Low** Insufficient evidence on differences in the risk for rare but severe adverse events. **Insufficient**
Biologic DMARDs plus oral DMARD other than MTX vs. biologic DMARDs	No difference in clinical response rates, functional capacity, and quality of life between etanercept plus sulfasalazine and etanercept monotherapy. **Low**	No differences in adverse events in efficacy studies. **Low** Insufficient evidence on differences in the risk for rare but severe adverse events **Insufficient**
Biologic DMARD plus MTX vs. MTX	Better clinical response rates, functional capacity, and quality of life from combination therapy of biologic DMARDs and MTX than from MTX monotherapy. **High** for clinical response and functional capacity, **Moderate** for quality of life	Better tolerability profile for MTX plus abatacept, adalimumab, certolizumab, etanercept, and rituximab than for MTX monotherapy from meta-analysis. **Low** Mixed evidence on differences in the risk for rare but severe adverse events. **Insufficient**

Key Comparisons	Efficacy Strength of Evidence	Harms Strength of Evidence
Strategies in Early RA		
Two oral DMARDs plus prednisone vs. oral DMARD	In patients on two oral DMARDs, improved ACR 50 response rates, disease activity scores, but no difference at 56 weeks. **Low** In patients with early RA, significantly lower radiographic progression and fewer eroded joints at 56 weeks. **Low** More rapid improvement in functional capacity by 28 weeks but no differences by 56 weeks. **Low**	No differences in discontinuation rates. **Moderate**
Three oral DMARDs plus prednisone vs. one oral DMARD	In patients on three oral DMARDs, improved ACR 50 response rates, disease activity scores, and less work disability. **Low** In patients with early RA, significantly lower radiographic progression and fewer eroded joints **Low**	No differences in discontinuation rates. **Moderate**
Sequential monotherapy starting with MTX vs. step-up combination therapy vs. combination with tapered high-dose prednisone vs. combination with infliximab	Less radiographic progression, lower disease activity scores, and better functional ability and health-related quality of life from initial combination therapy of MTX, sulfasalazine, and tapered high-dose prednisone or initial combination therapy with infliximab plus MTX than from sequential DMARD monotherapy or step-up combination therapy. However no differences between groups for functional ability and quality of life by 2 years and no difference in remission at 4 years. **Low**	No differences in serious adverse events between groups. **Low**

a. † at MTX doses ranging from 7.5-25 mg per week

4. Anmerkungen/Fazit der Autoren

Limited head-to-head comparative evidence does not support one therapy over another for adults with RA. Network meta-analyses from placebo-controlled trials of biologics suggest some differences, including higher odds of reaching ACR 50 response, but strength of evidence was low

5. Hinweise durch FB Med

- nicht immer eindeutige Angaben zur Vorbehandlung
- die meisten Studien waren von angemessener methodischer Qualität.

Machado MA et al., 2013 [27].

Adalimumab in rheumatoid arthritis treatment: a systematic review and meta-analysis of randomized clinical trials.

1. Fragestellung

Systematic review and meta-analysis of randomized controlled trials to evaluate the efficacy and safety of Adalimumab in the treatment of RA.

2. Methodik

Population: Erwachsene mit RA (nicht spezifiziert). Laut Angaben des Reviews sind zwei Studien in der Analyse enthalten, welche Therapienaive Patienten beinhalteten (GUEPARD und PREMIER Studie)

Interventionen, Kontrolle (Vergleiche): Adalimumab, etanercept, infliximab and rituximab

Endpunkte:

Primär:

ACR20 response defined by the ACR

Sekundär:

- ACR50 and ACR70 responses,
- in which there are 50% and 70% improvement in the same parameters,
- in addition to functionality,

- measured by the HAQ scale, radiographic outcomes, loss to follow-up and safety

Suchzeitraum (Aktualität der Recherche): Bis 06/2011

Anzahl eingeschlossene Studien/Patienten (Gesamt): 30 [Adalimumab: 11 (n = 3461); Infliximab: 10; Etanercept: 20; Rituximab: 14]

Qualitätsbewertung der Studien: Quality assessment by the modified Jadad scale and risk of bias assessment proposed by the Cochrane Collaboration were employed.

3. Ergebnisse

- Eleven articles related to adalimumab were included and considered nine studies with 3461 patients.

- 10 studies showed low risk of bias regarding the blinding of partici-pants and personnel and blinding of outcome assessment.

Table 2 – Risk of bias proposed by the Cochrane Collaboration[11] and modified Jadad scale score10 of the methodological quality of the studies included in the systematic review.

Study	Random generation of allocation sequence (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data	Selective reporting of outcomes	Modified Jadad scale
Van de Putte et al., 2004[24]	Low risk	Low risk	Low risk	Low risk	High risk	Uncertain	6
PREMIER (Breedveld 2006; Kimel 2008)[18,20]	Uncertain	Uncertain	Low risk	Low risk	Low risk	Low risk	5
DE019 (Keystone et al., 2004; Jamal et al.,2009)[21,22]	Uncertain	Uncertain	Low risk	Low risk	Low risk	Low risk	5
Kim et al., 2007[27]	Uncertain	Uncertain	Low risk	Low risk	Low risk	Low risk	5
ARMADA (Weinblatt et al., 2003)[16]	Uncertain	Uncertain	Low risk	Low risk	Low risk	Low risk	5
CHANGE (Miyasaka et al., 2008)[28]	Uncertain	Uncertain	Low risk	Low risk	Low risk	Low risk	5
Chen et al., 2009[23]	Uncertain	Uncertain	Low risk	Low risk	Low risk	Low risk	4
STAR (Furst et al., 2003)[17]	Uncertain	Uncertain	Low risk	Low risk	Low risk	Uncertain	4
GUEPARD (Soubrier et al., 2009)[19]	Uncertain	Uncertain	High risk	High risk	Low risk	Low risk	3

Efficacy:
Patients who received the combination treatment of adalimumab and methotrexate showed better efficacy results and lower radiographic progression when compared to placebo + methotrexate in 24-104 weeks.

Meta-analysis of ACR20, ACR50 and ACR70 responses in up to 24 weeks. Adalimumab 40 mg every two weeks + DMARDs vs. placebo + DMARDs:

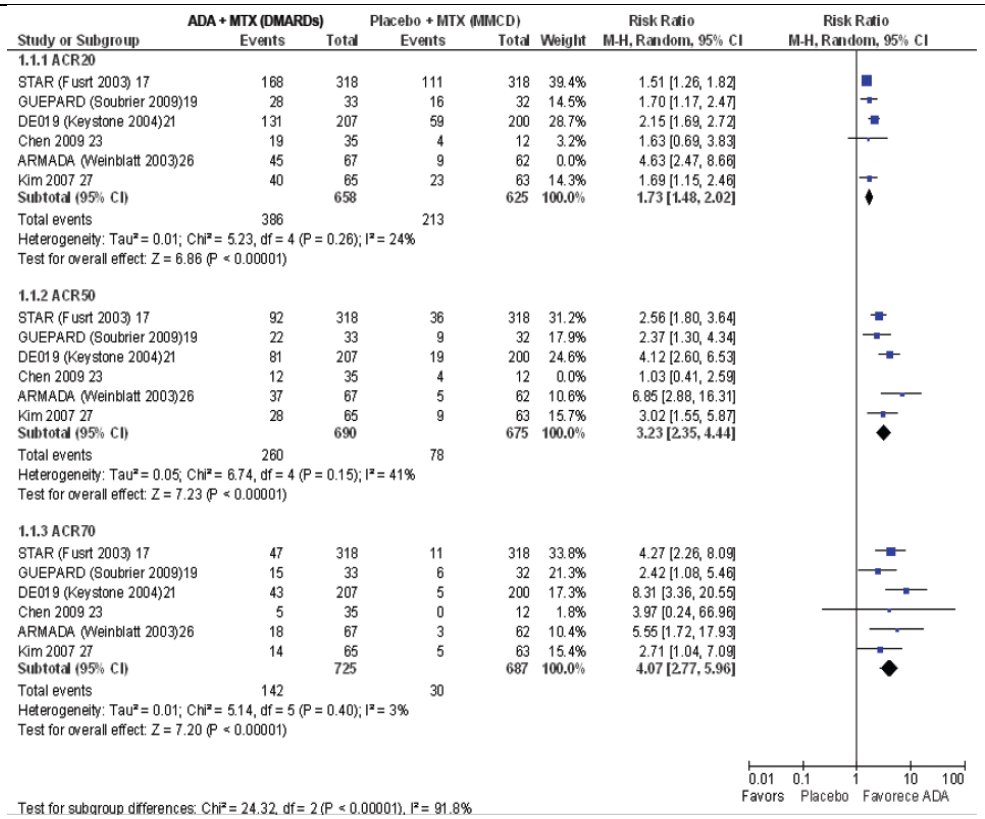


Fig. 2 – Meta-analysis of ACR20, ACR50 and ACR70 responses in up to 24 weeks. Adalimumab 40 mg every two weeks + DMARDs vs. placebo + DMARDs.
DMARDs, disease-modifying antirheumatic drugs; MTX, methotrexate. ADA, adalimumab.
Statistics I^2 >40% indicates statistical heterogeneity between the studies. A P value < 0.10 in the Chi-square test indicates heterogeneity.

Results of the meta-analyses for HAQ, AE and loss to follow-up for comparisons ADA 40 mg every two weeks+ DMARDs vs. placebo + DMARDs and ADA 40 mg every two weeks vs. placebo:

Outcome	Period (weeks)	Studies	Participants	Measure of effect (95%CI) *	I^2 (%)[a]	P value[b]
ADA 40 mg + MMCD vs. placebo + MMCD						
HAQ	Up to 24	4[19,21,26,27]	729	-0.32 (-0.40; -0.24)	0	0.99
HAQ	52	2[18,21]	932	-0.32 (-0.39; -0.24)	0	0.60
Loss due to lack of efficacy	Up to 104	4[17,18,21,27]	1696	0.31 (0.21; 0.45)	0	0.80
Loss due to adverse reaction	Up to 104	6[17,18,21,23,26,27]	1872	1.55 (1.08; 2.21)	0	0.61
Adverse reactions	Up to 104	5[17,18,21,23,27]	1955	1.03 (1.00; 1.05)	0	0.67
Severe adverse reactions	Up to 24	3[17,23,27]	811	0.84 (0.58; 1.20)	0	0.54
Infections	Up to 24	3[17,23,27]	1171	1.07 (0.93; 1.24)	0	0.59
Severe infections	Up to 104	6[17,18,21,23,26,27]	2014	1.73 (0.72; 4.14)	27	0.23
Reaction at the injection site	Up to 52	4[17,21,23,26]	1219	1.32 (1.02; 1.71)	2	0.38
Tuberculosis	Up to 104	5[17,18,21,23,27]	1743	2.25 (0.46; 11.02)	0	0.96
Cancer	Up to 104	6[17,18,21,23,26,27]	2226	1.02 (0.30; 3.47)	0	0.53
Death	Up to 104	5[17,18,21,23,27]	1743	2.38 (0.52; 10.84)	0	0.88
ADA 40 mg vs. placebo						
ACR20	24/26	2[24,28]	401	2.67 (1.89; 3.77)	0	0.45
HAQ	24/26	2[24,28]	401	-0.31 (-0.42; -0.19)	0	0.93
Loss due to adverse reaction	24/26	2[24,28]	401	3.34 (1.27; 8.80)	0	0.55
Severe adverse reactions	24/26	2[24,28]	401	1.24 (0.49; 3.13)	68	0.08
Reaction at the injection site	24/26	2[24,28]	401	12.45 (3.92; 39.52)	0	0.68

Safety:
The results of the meta-analyses of AEs were not statistically significant, except for reactions at the injection site, which favored the control group.

4. Anmerkungen/Fazit der Autoren

- Adalimumab efficacy was demonstrated in monotherapy and when associated to a DMARD, but the evidence for combined use is more robust.
- The results of the systematic review and meta-analysis showed that patients who were treated with ADA 40 mg every two weeks associated with MTX showed better efficacy results and lower radiographic progression when compared to patients receiving placebo + MTX. The risk of occurrence of loss to follow-up due to lack of efficacy was higher in the placebo + MTX group, while the loss due to adverse reactions was higher in the ADA + MTX group. However, these results are more robust for a follow-up of 24 weeks, as only two studies evaluated the patients for 52 and only one for 104 weeks
- There was no statistically significant difference regarding the efficacy and loss to follow-up due to lack of efficacy between the ADA monotherapy group with ADA 40 mg every two weeks and MTX monotherapy, whereas radiographic progression for the group that used ADA showed better results.
- The combination of ADA 40 mg every other week + MTX when compared to ADA 40 mg every two weeks as monotherapy showed better outcomes in ACR response and radiographic progression, whereas in the HAQ scale the result was statistically significant only at 52 weeks and also favorable to the combination. The risk of loss to follow-up due to lack of efficacy was higher for the monotherapy. These comparisons were evaluated by only one trial.
- The results of the meta-analyses of AEs were not statistically significant, except for reactions at the injection site, which favored the control group. Adalimumab efficacy was demonstrated in monotherapy and when associated to a DMARD, but the evidence for combined use is more robust.

	5. Hinweise der FB Med • Schweregrad der Erkrankung spielte keine Rolle bei der Auswertung der Primärstudien.
Golicki D et al., 2012 [14]. Leflunomide in monotherapy of rheumatoid arthritis: meta‑analysis of randomized trials	**1. Fragestellung** Evaluation der Wirksamkeit und Sicherheit von Leflunomid verglichen mit Placebo, MTX, und Sulfasalazin in der Monotherapie.
	2. Methodik Population: Patienten mit RA Intervention: Leflunomid Komparator: Placebo or any other active treatment Endpunkte: • ACR Ansprechen • Lebensqualität • Schmerzempfinden • Krankheitsaktivität • Laborparameter • Nebenwirkungen Suchzeitraum (Aktualität der Recherche): up to Dec 2011 Anzahl eingeschlossene Studien/Patienten (Gesamt): 7 (n = 2861) Qualitätsbewertung der Studien: Jadad scale.
	3. Ergebnisdarstellung ***Anzahl relevanter Studien/Patienten:*** 7 (n = 2861) • 1432 Patienten unter Leflunomid • 312 Patienten unter Placebo • 922 unter MTX • 133 unter Sulfasalazin Studiencharakteristika: siehe Tab

TABLE 1 Characteristics of included trials

Trial	Number and localization of centers	Population size	Duration of follow-up (weeks)	Population	Type of intervention (n)	Comparator (n)	Trial design	Assessment of trial quality by Jadad (points)
Mladenovic et al.[23]	6 Yugoslavia, Croatia, Slovenia	402	24	RA, active phase	LEF 5 mg/d (95) LEF 10 mg/d (101) LEF 25 mg/d (104)	placebo (102)	RCT, DB	4 (2/1/1)[a]
Smolen et al.[24]	36 Europe, Australia, New Zealand, South Africa	358	104	RA, active phase	LEF 20 mg/d (133)	placebo (92) sulfasalazine (133)	RCT, DB	5 (2/2/1)
Strand et al.[25]	47 United States, Canada	482	104	RA, active phase	LEF 20 mg/d (182)	placebo (118) MTX 7.5–15 mg/w (182)	RCT, DB	5 (2/2/1)
Emery et al.[26]	117 Europe, South Africa	999	104	RA, active phase	LEF 20 mg/d (501)	MTX 10–15 mg/w (498)	RCT, DB	4 (1/2/1)
Kraan et al.[27]	2 The Netherlands, United Kingdom	39	16	RA, active phase, early phase	LEF 20 mg/d (18)	MTX 15 mg/w (21)	RCT, DB	3 (1/1/1)
Kraan et al.[28]	2 The Netherlands	15	52	RA, active phase	LEF 20 mg/d (7)	MTX 7.5–15 mg/w (8)	RCT, DB	2 (1/1/0)
Bao et al.[29]	9 China	566	12	RA, active phase	LEF 20 mg/d (323)	MTX 15 mg/w (243)	RCT, DB	4 (1/2/1)

[a] summary Jadad scale depends on 3 factors: randomization (0–2 points; 1st figure in parentheses), blinding (0–2 points; 2nd figure in parentheses), and description of patients excluded from the study (0–1 point; 3rd figure in parentheses).

Wirksamkeit

Leflunomid vs. MTX:

- keine stat. signifikanten Unterschiede hinsichtlich einer Reduktion in den meisten Anzeichen und Symptomen der RA; bei jedoch allgemein hoher Heterogenität zwischen den Studien.
- Leflunomid zeigte teilweise (nicht zu jedem Zeitpunkt) eine stat. signifikante Überlegenheit gegenüber MTX hinsichtlich der Endpunkte: Anzahl an Patienten mit einem ACR 50 und ACR 70 Ansprechen (jeweils nach einem Jahr), der durch den Arzt beur-teilten Krankheitsaktivität (nach 12-16 Wochen), der Reduktion des C-reaktiv Protein (CRP) Levels (nach 12-16 Wochen), und der Verbesserung der Lebensqualität (gemessen anhand HAQ; nach 1 Jahr knapp und nach 2 Jahren).
- In den verbleibenden Endpunkten zeigte sich kein Unterschied zwischen den Gruppen.

FIGURE 2 Meta-analysis of efficacy of leflunomide vs. placebo: ACR20 responders

Abbreviations: ACR – American College of Rheumatology, CI – confidence interval

Study or subgroup	Leflunomide events	Leflunomide total	Methotrexate events	Methotrexate total	Weight	Risk ratio M-H, fixed, 95% CI
1.1.1 ACR50 – after 4 months of treatment						
Kraan et al.[28]	3	7	2	8	100%	1.71 [0.39–7.48]
subtotal (95% CI)		**7**		**8**	**100%**	**1.71 [0.39–7.48]**
total events	3		2			
heterogeneity: not applicable						
test for overall effect: Z = 0.72 (*P* = 0.47)						
1.1.2 ACR50 – after 1 year of treatment						
Kraan et al.[28]	5	6	5	7	9.5	1.17 [0.65–2.10]
Strand et al.[25]	65	190	44	190	90.5%	1.48 [1.07–2.05]
subtotal (95% CI)		**196**		**197**	**100%**	**1.45 [1.07–1.96]**
total events	70		49			
heterogeneity: $\chi^2 = 0.53$, df = 1 (*P* = 0.47); $I^2 = 0\%$						
test for overall effect: Z = 2.40 (*P* = 0.02)						
1.1.3 ACR50 – after 2 years of treatment						
Strand et al.[28]	65	190	53	190	100%	1.23 [0.91–1.66]
subtotal (95% CI)		**190**		**190**		**1.23 [0.91–1.66]**
total events	65		53			
heterogeneity: not applicable						
test for overall effect: Z = 1.33 (*P* = 0.19)						

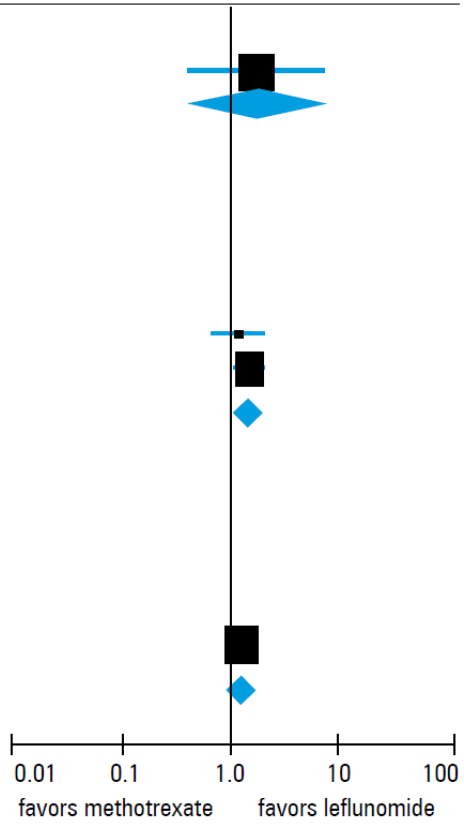


TABLE 3 Efficacy of leflunomide vs. methotrexate: summary of a meta-analysis

Endpoint	Number of trials	Number of patients	RR (95% CI)	Heterogeneity I^2
percentage of patients with ACR20 response				
– after 12–16 weeks	3[26,28,29]	558	1.04 (0.91–1.18)	0
– after 1 year	3[25,26,28]	1377	0.98 (0.73–1.32)	82.6
– after 2 years	2[25,26]	799	1.01 (0.77–1.32)	85.5
percentage of patients with ACR50 response				
– after 12–16 weeks	1[28]	15	1.71 (0.39–7.48)	–
– after 1 year	2[25,28]	393	1.45 (1.07–1.96)	0
– after 2 years	1[25]	380	1.23 (0.91–1.66)	–
percentage of patients with ACR70 response				
– after 1 year	1[25]	380	2.00 (1.20–3.34)	–
– after 2 years	1[25]	380	1.39 (0.85–2.29)	–
Endpoint	**Number of trials**	**Number of patients**	**WMD (95% CI)**	**Heterogeneity I^2**
reduction of tender joint count				
– after 12–16 weeks	2[27,29]	543	–1.42 (–3.96 to 1.12)	36.2
– after 1 year	2[25,26]	1346	0.21 (–2.24 to 2.66)	87.2
– after 2 years	2[25,26]	770	–0.16 (–1.87 to 1.54)	48.5
reduction of swollen joint count				
– after 12–16 weeks	2[27,29]	543	–0.40 (–1.17 to 0.38)	0
– after 1 year	2[25,26]	1346	0.99 (–1.46 to 3.44)	90.1
– after 2 years	2[25,26]	770	0.48 (–1.17 to 2.12)	57.8
patient's assessment of RA activity				
– after 12–16 weeks	2[27,29]	543	–0.23 (–0.72 to 0.27)	49.7
– after 1 year	2[25,26]	1346	0.03 (–1.15 to 1.20)	92.7
– after 2 years	2[25,26]	770	–0.30 (–1.37 to 0.78)	85.3
doctor's assessment of RA activity				
– after 12–16 weeks	2[27,29]	543	–0.35 (–0.67 to –0.02)	10.3
– after 1 year	2[25,26]	1346	0.13 (–0.84 to 1.11)	90.0
– after 2 years	2[25,26]	770	–0.01 (–1.28 to 1.26)	90.6
reduction in ESR				
– after 12–16 weeks	2[27,29]	543	1.60 (–6.42 to 9.62)	46.7
– after 1 year	2[25,26]	910	7.05 (–6.28 to 20.37)	95.0
– after 2 years	2[25,26]	747	7.51 (–3.74 to 18.76)	86.6
reduction in CRP levels				
– after 12–16 weeks	2[27,29]	543	–0.44 (–0.78 to –0.09)	0
– after 1 year	2[25,26]	907	0.03 (–0.37 to 0.44)	57.8
– after 2 years	2[25,26]	744	0.16 (–0.51 to 0.84)	28.3
patient's assessment of pain				
– after 12–16 weeks	2[27,29]	543	–0.38 (–0.74 to –0.01)	0
– after 1 year	2[25,26]	932	0.16 (–1.10 to 1.43)	91.9
– after 2 years	2[25,26]	769	–0.18 (–1.52 to 1.16)	89.5
duration of morning stiffness				
– after 12–16 weeks	2[27,29]	543	–16.59 (–43.99 to 10.80)	0
– after 1 year	2[25,26]	759	0.75 (–15.30 to 16.79)	66.8
– after 2 years	2[25,26]	759	8.28 (–8.72 to 25.28)	63.0
quality of life (HAQ) questionnaire				
– after 1 year	1[26]	530	0.06 (–0.02 to 0.14)	–
– after 2 years	1[26]	530	0.05 (–0.04 to 0.14)	–
quality of life (modified HAQ)				
– after 1 year	1[25]	362	–0.10 (–0.20 to 0.00)	–
– after 2 years	1[25]	199	–0.15 (–0.29 to –0.01)	–
progression of radiographic changes				
– after 1 year	2[25,26]	893	–0.03 (–0.85 to 0.78)	40.7
– after 2 years	1[25]	137	0.40 (–0.94 to 1.74)	–

Leflunomid vs. Sulfasalazin:
Es zeigte sich teilweise ein stat. signifikanter Vorteil unter Sulfasalazin hinsichtlich der Endpunkte: Reduktion der Erythrozyten-Sedimentationsrate (ESR) (nach einem halben Jahr); während Leflunomid stat. signifikant überlegen war hinsichtlich des ACR20 Ansprechen (nach 2 Jahren Krankheitsdauer) und ACR50 Ansprechen (nach 2 Jahren

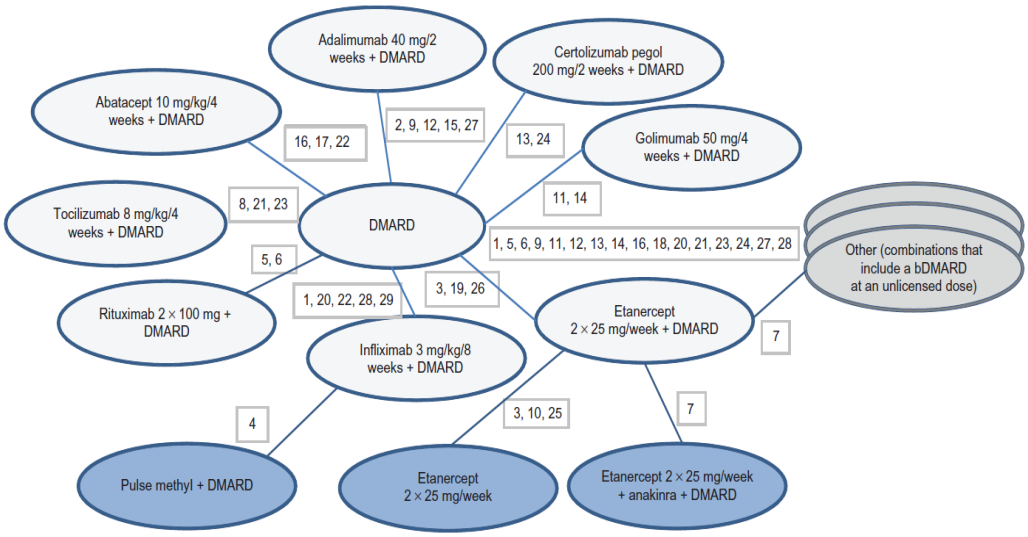
Behandlung), der Lebensqualität (gemessen anhand des HAQ; nach einem halben Jahr und nach 2 Jahren) und der CRP Level Reduktion (nach einem halben Jahr, einem Jahr und 2 Jahren).

TABLE 4 Efficacy of leflunomide vs. sulfasalazine: summary of the trial by Smolen et al.[24] and supporting publication – Scott et al.[35]

Endpoint	Number of patients	RR (95% CI)
percentage of patients with ACR20 response		
– after 0.5 year of treatment	262	0.99 (0.80–1.23)
– after 1 year of treatment	152	0.97 (0.78–1.20)
– after 2 years of treatment	117	1.37 (1.07–1.75)
percentage of patients with ACR50 response		
– after 0.5 year of treatment	262	0.98 (0.64–1.51)
– after 1 year of treatment	152	1.08 (0.74–1.59)
– after 2 years of treatment	117	2.10 (1.25–3.53)
percentage of patients with ACR70 response		
– after 0.5 year of treatment	262	1.52 (0.64–3.60)
– after 1 year of treatment	152	0.88 (0.44–1.75)
– after 2 years of treatment	117	1.43 (0.70–2.91)
Endpoint	**Number of patients**	**WMD (95% CI)**
reduction of tender joint count	262	–1.60 (–3.44 to 0.24)
reduction of swollen joint count	262	–13.40 (–14.89 to –11.91)
patient's assessment of RA activity	262	0.00 (–0.25 to 0.25)
doctor's assessment of RA activity	262	–0.10 (–0.32 to 0.12)
reduction in ESR		
– after 0.5 year of treatment	261	9.20 (3.47 to 14.93)
– after 1 year of treatment	150	8.10 (–0.13 to 16.33)
– after 2 years of treatment	114	–1.10 (–11.03 to 8.83)
reduction in CRP levels		
– after 0.5 year of treatment	260	–1.20 (–1.98 to –0.42)
– after 1 year of treatment	150	–1.10 (–2.17 to –0.03)
– after 2 years of treatment	111	–1.40 (–2.77 to –0.03)
patient's assessment of pain		
– after 0.5 year of treatment	262	–7.50 (–14.21 to –0.79)
– after 1 year of treatment	151	–11.40 (–20.35 to –2.45)
– after 2 years of treatment	117	–15.10 (–25.16 to –5.04)
duration of morning stiffness		
– after 0.5 year of treatment	262	–51.00 (–101.73 to –0.27)
– after 1 year of treatment	152	–76.00 (–135.49 to –16.51)
– after 2 years of treatment	165	–50.00 (–87.72 to –12.28)
quality of life (HAQ)		
– after 0.5 year of treatment	229	–0.21 (–0.34 to –0.08)
– after 1 year of treatment	128	–0.17 (–0.34 to 0.00)
– after 2 years of treatment	96	–0.29 (–0.49 to –0.09)
progression of radiographic changes		
– after 0.5 year of treatment	168	0.00 (–0.01 to 0.01)
– after 1 year of treatment	113	0.00 (–0.01 to 0.01)
– after 2 years of treatment	55	–0.04 (–0.19 to 0.11)

	Sicherheit: • **Leflunomid vs. MTX:** Verglichen mit MTX zeigte sich ein höheres Risiko unter Leflunomid hinsichtlich: Pruritus, Hypertension, Durchfall und Alopezie. Allerdings war das Risiko auf Schleimhautulzerationen und erhöhten Leberwerten geringer unter Leflunomide. • **Leflunomid vs. Sulfasalazin:** Höheres Risiko bei Rückenschmerzen und Durchfall unter Leflunomid verglichen mit Sulfasalazin. **TABLE 5** Summary of safety meta-analysis (only statistically significant comparisons showed) Adverse event | Number of trials | Number of patients | RR (95% CI) | Heterogeneity I^2 leflunomide vs. placebo alopecia | 3[23-25] | 832 | 5.79 (2.09–16.08) | 0 elevation of liver enzymes | 2[23-25] | 607 | 3.36 (1.71–6.63) | 0 withdrawal due to adverse events | 3[23-25] | 832 | 2.69 (1.64–4.41) | 0 diarrhea | 2[24,25] | 525 | 2,21 (1.48–3.32) | 0 allergic reactions | 1[25] | 300 | 1.68 (1.01–2.79) | – leflunomide vs. methotrexate pruritus | 2[26,29] | 1503 | 3.40 (1.72–6.74) | 0 hypertension | 2[25,26] | 1363 | 2.75 (1.76–4.29) | 0 diarrhea | 3[25,26,29] | 1867 | 2.01 (1.60–2.54) | 0 alopecia | 3[25,26,29] | 1867 | 1.62 (1.21–2.17) | 0 mouth ulceration | 2[25,26] | 1363 | 0.61 (0.38–0.96) | 0 elevation of liver enzymes >3 × ULN | 1[26] | 999 | 0.26 (0.18–0.37) | – leflunomide vs. sulfasalazine back pain | 1[24] | 266 | 3.67 (1.05–12.85) | – diarrhea | 1[24] | 266 | 1.92 (1.00–3.69) | – Abbreviations: UNL – upper normal limit, others – see TABLE 1
	4. Fazit der Autoren: There were no significant differences between the effects of treatment with leflunomide and methotrexate or sulfasalazine, but leflunomide monotherapy proved more effective than placebo in relieving symptoms and signs of RA. **5. Hinweise der FB Med** • Fazit weicht teilweise von der Ergebnisdarstellung ab • Nur zwei Studien bei ACR50 gepoolt • Dargestellte Ergebnisse (gepoolten ES) resultieren aus sehr wenigen Primärstudien
Aaltonen KJ et al., 2012 [1]. Systematic Review and Meta-Analysis of the Efficacy and Safety of Existing TNF Blocking Agents in Treatment of Rheumatoid	**1. Fragestellung** The aim of our study is to estimate the efficacy and the safety of TNF blockers in the treatment of RA and indirectly compare all five currently available blockers by combining the results from included RCTs.
	2. Methodik Systematischer Review/ Metaanalyse von RCT ***Population:*** Erwachsene mit RA ***Interventionen / Kontrolle*:** TNF-blockers vs. placebo, with or without concomitant MTX ***Endpunkte***: Efficacy data included ACR 20%, 50% and 70% improvements; safety ***Suchzeitraum (Aktualität der Recherche):*** Bis 06/2010 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 26 (n = 9862)

Arthritis.	***Qualitätsbewertung der Studien:*** Cochrane Risk of Bias
	3. Ergebnisse • Most Studies with an unclear risk of bias • Studienpopulationen: sowohl MTX-naïve als auch MTX erfahrene Patienten ***Wirksamkeit*** Kombination therapy • Kombination (TNFi + MTX) signifikant besser als MTX Monotherapie bzgl. ACR20, ACR50, ACR70 zu verschiedenen Zeitpunkten (3, 6, 12 Monate) • In a subanalysis of trials with patients who had previously used MTX, the results were similar. In comparison to MTX, golimumab combination therapy was still inferior in ACR 20 efficacy at 6 months to certolizumab combination therapy, with risk ratios of 2.14 (1.59–2.89) and 5.08 (3.46–7.48), respectively. • At six months patients previously naive to MTX are statistically significantly less likely to reach either ACR 20, 50 or 70 treatment responses compared to patients who had already been previously treated with MTX. Monotherapy • Monotherapie mit TNF-Blockern tendenziell besser als MTX-Monotherapie, aber Ergebnisse nicht statistisch signifikant., • Stratifying RTCs by previous exposure to MTX does not show any statistically significant differences in the treatment response to TNF-blocker monotherapy between these two groups ***Sicherheit***: • TNF-Blocker + MTX vs. MTX – mehr Nebenwirkungen bei Kombi-nationstherapie bzgl. Therapieabbruch und Infusions-/Injektions-Reaktionen • TNF-Blocker vs. MTX: mehr Nebenwirkungen bei TNF-Blocker bei Infusions-/Injektions-Reaktionen
	4. Fazit der Autoren: No single substance clearly rose above others in efficacy, but the results of the safety analyses suggest that etanercept might be the safest alternative. Interestingly, MTX performs nearly identically considering both efficacy and safety aspects with a margin of costs. **5. Hinweise der FB Med** • Schweregrad der Erkrankung spielte keine Rolle bei der Auswertung der Primärstudien
Orme ME et al., 2012 [34]. Systematic review and network meta-analysis of combination and monotherapy treatments in disease-modifying antirheumatic	**1. Fragestellung** Wirksamkeit von EU licensed-dose Biologica-Kombinationen bei RA Patienten mit unzureichendem Ansprechen auf ein oder mehrere DMARDs
	2. Methodik SR/Metaanalyse/indirekter Vergleich (nach Bucher) von RCTs ***Population:*** Adult patients meeting the ACR classification criteria for RA, previously treated with MTX or other DMARD, <=15% of patients previously treated with TNF-α inhibitors ***Intervention*** Any bDMARD licensed in the EU Studies needed to include at least one treatment arm of bDMARD in combination with a DMARD or as a monotherapy ***Komparator*** (combination analysis) or placebo (monotherapy analysis)

drug-experienced patients with rheumatoid arthritis	***Endpunkte***: ACR 20/50/70 response rates Outcome reported between 12 and 30 weeks of follow-up ***Suchzeitraum (Aktualität der Recherche):*** Bis 05/2010 ***Anzahl* eingeschlossene Studien/Patienten *(Gesamt):*** Einschluss von 37 Studien (23 nur Kombi-Therapie, 8 nur Monotherapie, 6 beides) ***Qualitätsbewertung der Studien:*** Risk of bias was assessed using criteria set out in the National Institute for Health and Clinical Excellence (NICE) guidelines manual. For studies included in the meta-analysis, a formal assessment of publication bias was conducted via funnel plots with Egger's linear regression test of asymmetry.
	3. Ergebnisdarstellung: *Study characteristics/ quality of studies* • patients had active RA in spite of prior treatment with a DMARD; (moderate to severe disease) • in most trials, the patient population was anti-TNFα inhibitor-naïve • The definition of "active RA" was inconsistent across studies • The risk of bias, as assessed by NICE criteria, was considered low for the majority of included studies. For five studies, the risk of bias was unclear, due to incomplete reporting. Only the study by van Riel et al47 was considered to have a high risk of bias, as there was no concealment of treatment allocation (and several other parameters were unclear). Netzwerk-Meta-analyse zur Kombinationstherapie:  **Figure 2** Network diagram for ACR20/50/70 outcomes for bDMARD combination therapies. **Notes: 1,** Abe 2006; 2, Chen 2009; 3, Combe 2006; 4, Durez 2004; 5, Edwards 2004; 6, Emery 2010 (SERENE); 7, Genovese 2004; 8, Genovese 2008 (TOWARD); 9, Huang 2009; 10, Kameda 2010 (JESMR); 11, Kay 2008; 12, Keystone 2004 (DE019); 13, Keystone 2008 (RAPID 1); 14, Keystone 2009 (GO-FORWARD); 15, Kim 2007; 16, Kremer 2003; 17, Kremer 2006 (AIM); 18, Kremer 2010; 19, Lan 2004; 20, Maini 1999 (ATTRACT); 21, Maini 2006 (CHARISMA); 22, Schiff 2008 (ATTEST); 23, Smolen 2008 (OPTION); 24, Smolen 2009a (RAPID 2); 25, van Riel 2006 (ADORE); 26, Weinblatt 1999; 27, Weinblatt 2003 (ARMADA); 28, Westhovens 2006b (START); 29, Zhang 2006. DMARD 25 arms, 3039 patients; abatacept 10 mg/kg/4 weeks + DMARD 3 arms, 704 patients; adalimumab 40 mg/2 weeks + DMARD 5 arms, 495 patients; certolizumab pegol 200 mg/2 weeks + DMARD 2 arms, 639 patients; etanercept 2 × 25 mg/week + DMARD 6 arms, 500 patients; golimumab 50 mg/4 weeks + DMARD 2 arms, 124 patients; infliximab 3 mg/kg/8 weeks + DMARD 6 arms, 760 patients; rituximab 2 × 1000 mg + DMARD 2 arms, 212 patients; tocilizumab 8 mg/kg/4 weeks + DMARD 3 arms, 1058 patients. Netzwerk-Meta-Analyse zur Monotherapie

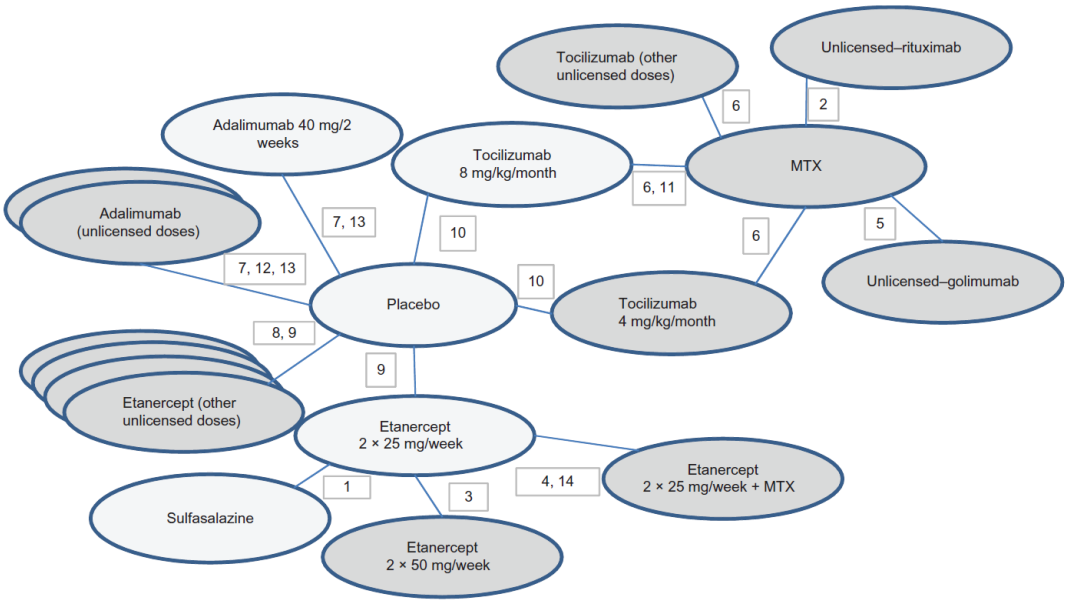


Figure 6 Network diagram for ACR20/50/70 outcomes for bDMARD monotherapy.
Notes: 1, Combe 2006; 2, Edwards 2004; 3, Johnsen 2006; 4, Kameda 2010 (JESMR); 5, Keystone 2009 (GO-FORWARD); 6, Maini 2006 (CHARISMA); 7, Miyasaka 2008 (Change); 8, Moreland 1997; 9, Moreland 1999; 10, Nishimoto 2004 (STREAM); 11, Nishimoto 2009 (SATORI); 12, van de Putte 2003; 13, van de Putte 2004; 14, van Riel 2006 (ADORE). Placebo 6 arms, 444 patients; MTX 4 arms, 488 patients; etanercept 2 × 25 mg/week, 5 arms, 441 patients; tocilizumab 8 mg/kg/4 weeks, 3 arms, 168 patients; adalimumab 40 mg/2 weeks, 2 arms, 204 patients; sulfasalazine 1 arm, 50 patients.

- Results
  - Kombination aus bDMARD + DMARD signifikant besser bzgl. ACR20/50/70 als DMARD allein (außer Rituximab bei ACR70)
  - Etanercept Kombination signifikant besser als Adalimumab, Infliximab, Abatacept Kombinationen bzgl. ACR20/50/70
  - keine signifikanten Unterschiede zwischen Etanercept-Kombination und Certolizumab pergol oder Tocilizumab-Kombinationen
  - Monotherapie mit Etanercept signifikant besser als Sulfasalazin bzgl. ACR 20/50/70

Table 6 American College of Rheumatology (ACR) criteria scores of 20, 50, and 70 network meta-analysis base case results for combination treatments in DMARD-experienced patients: licensed ETN combination versus other licensed biologic DMARD combination

Treatment	Control	Fixed effects OR v control (95% CrI)	Random effects OR v control (95% CrI)
ACR 20			
ETN 2 × 25 mg/week + DMARD	ABA 10 mg/kg/4 weeks + DMARD	2.715 (1.521, 4.956)‡	2.858 (1.306, 6.815)‡
ETN 2 × 25 mg/week + DMARD	ADA 40 mg/2 weeks + DMARD	2.53 (1.405, 4.742)‡	2.72 (1.235, 6.357)‡
ETN 2 × 25 mg/week + DMARD	CZP 200 mg/2 weeks + DMARD	0.836 (0.437, 1.613)	0.846 (0.341, 2.173)
ETN 2 × 25 mg/week + DMARD	GOL 50 mg/4 weeks + DMARD	2.546 (1.235, 5.249)‡	2.759 (1.066, 7.88)‡
ETN 2 × 25 mg/week + DMARD	INF 3 mg/kg/8 weeks + DMARD	2.651 (1.509, 4.791)‡	2.786 (1.299, 6.301)‡
ETN 2 × 25 mg/week + DMARD	RTX 2 × 1000 mg + DMARD	2.48 (1.278, 4.958)‡	2.521 (0.966, 6.711)
ETN 2 × 25 mg/week + DMARD	TOC 8 mg/kg/4 weeks + DMARD	1.987 (1.115, 3.602)‡	2.121 (0.959, 5.107)
ACR 50			
ETN 2 × 25 mg/week + DMARD	ABA 10 mg/kg/4 weeks + DMARD	2.871 (1.395, 6.523)‡	3.07 (1.161, 8.969)‡
ETN 2 × 25 mg/week + DMARD	ADA 40 mg/2 weeks + DMARD	2.625 (1.249, 6.101)‡	2.882 (1.082, 8.347)‡
ETN 2 × 25 mg/week + DMARD	CZP 200 mg/2 weeks + DMARD	1.144 (0.492, 2.847)‡	1.143 (0.358, 3.715)
ETN 2 × 25 mg/week + DMARD	GOL 50 mg/4 weeks + DMARD	2.264 (0.924, 5.999)‡	2.277 (0.672, 7.943)
ETN 2 × 25 mg/week + DMARD	INF 3 mg/kg/8 weeks + DMARD	2.896 (1.426, 6.583)‡	3.098 (1.186, 8.671)‡
ETN 2 × 25 mg/week + DMARD	RTX 2 × 1000 mg + DMARD	2.662 (1.109, 6.817)‡	2.714 (0.826, 9.174)
ETN 2 × 25 mg/week + DMARD	TOC 8 mg/kg/4 weeks + DMARD	1.759 (0.849, 4.018)	2.068 (0.766, 6.284)
ACR 70†			
ETN 2 × 25 mg/week + DMARD	ABA 10 mg/kg/4 weeks + DMARD	5.405 (1.348, 39.22)‡	5.278 (1.016, 46.3)‡
ETN 2 × 25 mg/week + DMARD	ADA 40 mg/2 weeks + DMARD	4.826 (1.171, 34.53)‡	5.45 (1.07, 45.914)‡
ETN 2 × 25 mg/week + DMARD	CZP 200 mg/2 weeks + DMARD	1.661 (0.329, 13.06)	1.636 (0.244, 14.84)
ETN 2 × 25 mg/week + DMARD	GOL 50 mg/4 weeks + DMARD	4.055 (0.796, 31.279)	4.312 (0.604, 48.757)
ETN 2 × 25 mg/week + DMARD	INF 3 mg/kg/8 weeks + DMARD	5.395 (1.358, 38.16)‡	5.642 (1.126, 48.13)‡
ETN 2 × 25 mg/week + DMARD	RTX 2 × 1000 mg + DMARD	7.924 (1.686, 59.453)‡	8.058 (1.225, 78.37)‡
ETN 2 × 25 mg/week + DMARD	TOC 8 mg/kg/4 weeks + DMARD	2.385 (0.593, 16.28)	2.766 (0.535, 25.2)

Notes: †ACR 70 data with continuity correction; ‡licensed ETN combination has significantly higher odds of ACR outcome compared to other licensed biologic DMARD combination (based on the 95% CrI).
Abbreviations: ABA, abatacept; ADA, adalimumab; ANA, anakinra; CrI, credible interval (Bayesian probability interval); CZP, certolizumab pegol; DMARD, disease-modifying antirheumatic drug (MTX or SUL); ETN, etanercept; exp, experienced; GOL, golimumab; INF, infliximab; MTX, methotrexate; OR, odds ratio; RTX, rituximab; SUL, sulfasalazine; TOC, tocilizumab.

4. Fazit der Autoren:
Licensed bDMARDs are efficacious in patients with an inadequate response to conventional therapy, but TNF-α inhibitor combination therapies are not equally effective.

5. Hinweise der FB Med
- Schweregrad der Erkrankung spielte keine Rolle bei der Auswertung der Primärstudien.

Lee YH et al., 2011 [23]. The efficacy and safety of rituximab for the treatment of active rheumatoid arthritis: a systematic review and meta-analysis of randomized controlled trials.

1. Fragestellung
The aims of this study were to assess the efficacy and safety of rituximab in patients with active RA.

2. Methodik

Population: patients with active RA; intolerant or resistant to DMARD or TNF-blocker

Interventionen: Rituximab + MTX
Kontrolle: placebo + MTX
Endpunkte: ACR 20, 50, 70 – Ansprechrate

Suchzeitraum (Aktualität der Recherche): Bis 12/2009

Anzahl eingeschlossene Studien/Patienten (Gesamt): 3 (n = 938 Pat.)

Qualitätsbewertung der Studien: assessment of concealment of treatment allocation, blinding, and adequacy of analyses

3. Ergebnisdarstellung

Studiencharakteristika:

Table 1 Characteristics of the studies included in the meta-analysis

Study	Country	Study design (name)	Patient number (intention to treat)	RF positivity (%)	Subjects	Treatments (numbers)	Follow-up period	ACR20, 50, 70 (%)
A								
Cohen et al. [11]	UK	RCT (REFLEX)	517 (499)	79	Active RA inadequate response or intolerant to anti-TNF	Rituximab +MTX (298) versus placebo + MTX (201)	24 weeks	51, 27, 12 versus 18, 5, 1
Emery et al. [12]	UK	RCT (DANCER)	341 (244)	82	Active RA, failure to DMARDs, biologic response modifiers	Rituximab +MTX (122) versus placebo + MTX (122)	24 weeks	54, 34, 20 versus 28, 13, 5
Edwards et al. [13]	UK	RCT	80 (80)	100	Active RA despite current MTX	Rituximab + MTX (40) versus placebo + MTX (40)	48 weeks	65, 35, 15 versus 20, 5, 0

Study	Concealment of allocation	Placebo control	Patient blinding	Intention-to-treat analysis	Patients randomly assigned	Duration of follow-up
B						
Cohen et al. [11]	Unclear	Adequate	Adequate	Adequate	Adequate	24 weeks
Emery et al. [12]	Unclear	Adequate	Adequate	Adequate	Adequate	24 weeks
Edwards et al. [13]	Unclear	Adequate	Adequate	Adequate	Adequate	48 weeks

RF rheumatoid factor, *RCT* randomized controlled trial, *REFLEX* randomized evaluation of long-term efficacy of rituximab, *DANCER* dose-ranging assessment international clinical evaluation of rituximab in rheumatoid arthritis, *TNF* tumor necrosis factor, *DMARD* disease modifying anti-rheumatic drug, *RA* rheumatoid arthritis, *MTX* methotrexate, *ACR20, 50, and 70* American College of Rheumatology 20, 50, and 70% response rates

- ACR20, ACR50, and ACR70 response rates were significantly higher for rituximab plus MTX-treated patients than for MTX plus placebo-treated patients (ACR50; RR 3.648, 95% CI 2.478–5.369)
- Regarding safety, rituximab was not found to be associated with any increase in AEs. Furthermore, no significant difference was observed between rituximab plus MTX and MTX plus placebo controls with respect to the proportions of patients that experienced at least one SAE.

4. Fazit der Autoren:

A single course of rituximab with concomitant MTX therapy was found to be effective in DMARD or TNF-blocker-resistant or intolerant patients with active RA.

5. Hinweise der FB Med

- Schweregrad der Erkrankung spielte keine Rolle bei der Auswertung der Primärstudien.
- nur 3 Primärstudien eingeschlossen
- keine Langzeitstudien

	• beträchtliche qualitative und hohe quantitative Heterogenität zwischen den Primärstudien
Jansen JP et al., 2014 [19]. Comparative efficacy of biologics as monotherapy and in combination with methotrexate on patient reported outcomes (PROs) in rheumatoid arthritis patients with an inadequate response to conventional DMARDs – a systematic review and network meta-analysis.	**1. Fragestellung** To compare biologics as monotherapy or in combination with methotrexate (MTX) in terms of patient reported outcomes (PROs) in RA patients with an inadequate response to conventional DMARDs (DMARD-IR).
	2. Methodik ***Population:*** DMARD-IR RA patients ***Intervention:*** Tocilizumab, TNF-blockers, abatacept, and anakinra in their usual dose, alone and in combination with conventional DMARDs. Rituximab was not considered because its label is restricted to TNF-IR patients. Tofacitinib was not included because it was not approved at the time of this study ***Kontrolle:*** Placebo or one of the regimes described under interventions. Comparisons of different dosages of the same intervention only, or comparison of the same interventions with different background treatments were excluded ***Endpunkte:*** HAQ-DI, Pain, PGA, SF36, and fatigue ***Suchzeitraum (Aktualität der Recherche):*** Systematische Literaturrecherche bis 2012 ***Anzahl eingeschlossener Studien/Patienten (Gesamt):*** A total of 26 full text reports corresponding to 20 different RCTs. ***Qualität der Studien:*** Most of the trials were multi-centred and included patients predominantly from Europe and North America. The RCTs were generally considered to be good quality (Jadad score range 3–5).
	3. Ergebnisdarstellung <u>In general:</u> To synthesize the results of the included studies, Bayesian network meta-analysis models were used! → Ergebnisse basieren auf indirekter Evidenz! For the analysis we grouped the different aTNFs because previous analysis demonstrated that the different aTNFs are exchangeable **Monotherapy:** • Tocilizumab monotherapy showed greater improvements in pain (−11.1; 95% CrI −21.3, −0.1) than aTNF as monotherapy, and can be expected to be more efficacious in terms of PGA as well (−10.3, 95% CrI −20.4, 0.8; probability better = 97%). • Tocilizumab was at least as efficacious as aTNF agents in HAQ-DI improvements (−0.16; 95% CrI −0.37, 0.05; probability better = 94%) • Given the available studies, no comparison of SF36 for the biologics as monotherapy was possible. **Treatment in combination with methotrexate:** • aTNF (−17.9, −19.1), abatacept (−23.0, −13.6) and tocilizumab (−16.0, −15.1) in combination with MTX showed comparable reductions in pain and PGA relative to MTX in this DMARD-IR population. • These improvements over MTX are expected to be greater than the MCID. The reduction in pain and PGA with anakinra (−7.3, −8.7) was smaller.

	• Regarding HAQ-DI, the greatest improvements over MTX can be expected with aTNF (−0.30) and tocilizumab (−0.27), both clinically meaningful, followed by abatacept (−0.21) and anakinra (−0.11). Improvements in physical health according to the SF36-PCS with abatacept, aTNF and tocilizumab were comparable. **Comparison of monotherapy and treatment in combination with methotrexate:** • There is a 93% and 96% probability that aTNF in combination with MTX results in a greater reduction in pain (−12.4) and PGA (−16.1) than aTNF as monotherapy. These differences are expected to be greater than the MCID. • For HAQ-DI there is a 92% chance that aTNF with MTX is more efficacious than aTNF as monotherapy (−0.21). For tocilizumab however, the improvement in pain, PGA, and HAQ-DI with and without MTX was comparable at 24 weeks. • Efficacy of anakinra + MTX was much smaller as compared to other biologics. • The greatest improvements in HAQ-DI relative to MTX were observed with aTNF + MTX (−0.30 (−0.37, −0.22)) and tocilizumab + MTX (−0.27 (−0.42, −0.12)), followed by abatacept + MTX (−0.21 (−0.37, −0.05)) and anakinra + MTX (−0.11 (−0.26, 0.05)). • There is a >90% probability that aTNF +MTX results in a greater improvement in pain (−12.4), PGA (−16.1) and HAQ-DI (−0.21) than aTNF as monotherapy. • Efficacy of tocilizumab + MTX showed comparable improvements in PROs as tocilizumab monotherapy.
	4. Fazit der Autoren: Based on a network meta-analysis involving indirect comparison of trial findings, the following observations were made for DMARD-IR patients. In monotherapy, tocilizumab was associated with a greater improvement in pain and self-reported disease activity than aTNF, and was at least as efficacious regarding functional ability. The improvements in PROs with aTNF, abatacept and tocilizumab in combination with MTX were comparable. Improvements in PROs with tocilizumab as monotherapy were similar to that of tocilizumab +MTX, whereas aTNF as monotherapy was likely to be less efficacious than aTNF + MTX.
Scott DL et al., 2014 [38]. Randomised controlled trial of Tumour necrosis factor inhibitors Against Combination Intensive Therapy with conventional disease-modifying antirheumatic drugs in established rheumatoid arthritis: the TACIT trial	**1. Fragestellung** (HTA programme) We assessed whether or not combination DMARDs (cDMARDs) give equivalent clinical benefits at lower costs in RA patients eligible for TNFis. • We assessed whether or not RA patients eligible to receive TNFis achieve similar outcomes with cDMARDs in a head-to-head trial that compared both approaches [Tumour necrosis factor inhibitors Against Combination Intensive Therapy (TACIT)]. • We also systematically reviewed published trials that assessed the efficacy of cDMARDs, TNFis with methotrexate and both approaches in patients with active RA.
	2. Methodik des SR ***Population:*** Early and established RA patients • *Early RA:* disease duration was < 3 years • *Established RA:* patients were treatment resistant to at least one previous DMARD given for at least 3 months ***Intervention:*** • *Early RA:* one or other or both of cDMARDs and TNFi/MTX • *Established RA*: one or other or both of cDMARDs and TNFi/MTX; when more than one dosage of TNFi was used the treatment arm that mirrored clinical practice the closest was chosen

and associated systematic reviews.	***Komparator:*** DMARD monotherapy ***Endpunkte:*** American College of Rheumatology responses, withdrawals (for inefficacy), diability (HAQ score) ***Suchzeitraum (Aktualität der Recherche):*** Ovid MEDLINE and EMBASE were searched from 1946 to 2013. ***Anzahl eingeschlossener Studien/Patienten (Gesamt):*** 32 für early RA; 19 für established RA ***Qualität der Studien:*** Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions. Methods Guide for Comparative Effectiveness Review. (AHRQ Publication) Heterogeneity: The cDMARD trials showed no evidence of heterogeneity in ACR20–70 scores. In contrast, the TNFi trials showed significant heterogeneity in ACR20 scores ($p < 0.00001$) and ACR50 scores ($p < 0.0002$) and borderline heterogeneity in ACR70 scores ($p = 0.06$).
	3. Ergebnisdarstellung **SR of early RA** • 19 trials compared cDMARDs with methotrexate • 10 trials compared TNFis/methotrexate with methotrexate monotherapy • 3 trials compared cDMARDs with TNFis/methotrexate *American College of Rheumatology responses and withdrawals for inefficacy* Indirect comparisons showed that in trials of DMARD combinations more patients achieved ACR20–70 responses with combination therapy (OR 1.76–2.81) and less patients withdrew because of inefficacy with combination therapy (OR 0.47, 95% CI 0.34 to 0.64). In trials of TNFi/methotrexate combinations more patients achieved ACR20–70 responses with combination therapy (OR 1.88–2.22) and fewer patients withdrew because of inefficacy with combination therapy (OR 0.44, 95% CI 0.22 to 0.85). Sensitivity analysis of trials using only methotrexate monotherapy showed similar results. Direct comparisons showed that there were no differences between DMARD combinations and TNFi/methotrexate with regard to ACR20 outcomes or patient withdrawals because of inefficacy. However, fewer patients achieved ACR50 and ACR70 responses using cDMARDs than using TNFi/methotrexate (ORs 0.54 and 0.53 respectively). Overall, there were small differences in favour of TNFi/methotrexate compared with cDMARDs at most time points but these were not always significant. There were also marked differences in response rates in the different trials. *Disability* In the indirect comparisons there were greater improvements in HAQ scores with both combination regimens when compared with DMARD monotherapy (OR −0.15, 95% CI −0.23 to −0.07) or methotrexate monotherapy (OR −0.17, 95% CI −0.33 to −0.01). No RCTs that made a direct comparison between cDMARDs and TNFi/methotrexate reported HAQ outcomes. *Toxicity* Indirect comparisons showed that more patients withdrew with DMARD combinations because of toxicity than with DMARD monotherapy (OR 1.50, 95% CI 1.11 to 2.03) or

	with methotrexate monotherapy (OR 2.69, 95% CI 1.49 to 4.83). There were no differences between TNFi/methotrexate and methotrexate monotherapy in terms of withdrawals because of toxicity. The direct comparisons showed no differences in patient withdrawal because of toxicity **<u>SR of established RA:</u>** • 10 trials compared cDMARDs with DMARD monotherapy, of which six used methotrexate monotherapy as the control arm, • Eight trials compared TNFi/methotrexate with methotrexate monotherapy,with one involving infliximab, two etanercept, one adalimumab, two golimumab and two certolizumab pegol. • one trial made a direct comparison between methotrexate/sulfasalazine/hydroxychloroquine and etanercept/methotrexate. <u>Wirksamkeit</u> *American College of Rheumatology responses and withdrawals for inefficacy* • In trials of DMARD combinations more patients achieved ACR20–70 responses with combination therapy (OR 2.75–5.07). • More patients withdrew with combination therapy (OR 1.51, 95% CI 1.02 to 2.25). • Sensitivity analysis of RCTs that included a methotrexate monotherapy arm showed that more patients achieved ACR20–70 responses with combination therapy (OR 3.55–4.74) but few patients withdrew because of inefficacy (OR 0.34, 95% CI 0.20 to 0.59). • In trials of TNFi/methotrexate combinations more patients achieved ACR20–70 responses with combination therapy (OR 5.32–8.13) • Fewer patients withdrew because of inefficacy with combination therapy (OR 0.12, 95% CI 0.06 to 0.25). • The trial comparing triple DMARD therapy with etanercept/MTX237 showed no statistical difference between groups in ACR20 (57% vs. 66%), ACR50 (35% vs. 43%) and ACR70 (18% vs. 26%). This study did not report patient withdrawals for inefficacy. *Disability* • Five randomised trials of cDMARDs reported change in HAQ scores • Only three of these trials reported both mean changes and SDs for these changes. • A combined analysis of these three trials' HAQ scores showed that, overall, there were greater improvements with cDMARDs than with DMARD monotherapy (WMD −0.19, 95% CI −0.27 to −0.10). • Only one of these RCTs used methotrexate as the monotherapy this trial also showed greater improvement with cDMARDs (WMD −0.30, 95% CI −0.42 to −0.18). • For TNFi/methotrexate combinations five trials reported change in HAQ scores • In all of these trials there was an improvement in HAQ score in the combination arm. • One trial reported mean (SD) change in HAQ score (WMD −0.35, 95% CI −0.56 to −0.14). • The trial that made a direct comparison between methotrexate/sulfasalazine/hydroxychloroquine and etanercept/methotrexate reported mean HAQ scores at 48 weeks. • There was no difference in HAQ scores between triple DMARD therapy (0.93 ± 0.85) and etanercept/methotrexate (0.83 ± 0.81). <u>Sicherheit</u>:

	• For cDMARDs, all 10 trials reported patient withdrawals because of toxicity. • The overall OR for withdrawal with combination therapy was 1.51 (95% CI 1.02 to 2.25). Seven of these studies used methotrexate as the monotherapy arm; the OR for withdrawal was 1.58 (95% CI 0.97 to 2.59). • For TNFi/methotrexate combinations, eight trials reported patient withdrawals because of toxicity. • There were no significant differences between treatments, with an OR of 0.94 (95% CI 0.62 to 1.41). • The direct comparison trial did not report patient withdrawals because of toxicity.
	4. Fazit und Anmerkungen der Autoren Systematic reviews of published trials in both early RA and established RA show equivalence of cDMARDs with TNFis. • Only three RCTs directly compared cDMARDs with TNFi/methotrexate combinations and all of these were in early RA. Although we have relied more on indirect comparisons, these are invariably less informative than direct comparisons. • There was diversity in the range of cDMARDs used and some are not commonly used in clinical practice, for example bucillamine and doxycycline.
Schoels M et al., 2012 [37]. Comparative effectiveness and safety of biological treatment options after tumour necrosis factor α inhibitor failure in rheumatoid arthritis: systematic review and indirect pairwise meta-analysis	**1. Fragestellung** Optimal treatment for RA after inadequate response (IR) to tumour necrosis factor (TNF) α inhibitors remains uncertain. Objective: To compare the efficacy and safety of biological agents after TNF α inhibitors IR.
	2. Methodik SR mit placebokontrollierten RCTs und indirektem Vergleich (Brückenkomparator: Placebo) ***Population:*** Adult RA populations with an inadequate therapeutic response to one or more TNF inhibitors ***Intervention***: a new biological treatment (combined with synthetic DMARD) ***Kontrolle:*** Placebo using synthetic DMARDs only ***Outcomes*** • Efficacy was defined as rates of ACR (20%, 50% and 70%) response, EULAR response criteria, or achieving remission (or a low disease activity state). • Safety outcomes extracted at the study level included any AEs, SAEs, serious infections and infusion- or injection-related reactions after a follow-up of ≥ 8 weeks. ***Suchzeitraum (Aktualität der Recherche):*** Bis 03/2011 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 4 (n = 1873) ***Qualitätsbewertung der Studien:*** Jadad Scale
	3. Ergebnisdarstellung *Studiencharakeristika:*

Table 1 Patient baseline characteristics

Treatment/study, year of publication	Co-medication (DMARD)	Patient (N)	Age (years)‡	Disease duration (years)	Female (%)	HAQ-DI‡	SJC‡	TJC‡	DAS28‡	Jadad score
ABA* Genovese ATTAIN; 2005	75% MTX*	393	53.4±12.4	12.2±8.5	77.1	1.8±0.6	22.3±10.2	31.2±13.0	6.5±0.9	3
GOL Smolen GO-AFTER 50 mg; 2009	†66% MTX	461 (all) (†304)	55.0 (46.0–63.0)§	9.6 (5.6–17.2)§	74	1.6 (1.1-2.0) (all) (†1.5 (1.1–1.9))§	14.0 (9.0–25.0)§	27.0 (16.0–42.0)§	6.3 (5.6–7.2)§	4
RTX Cohen REFLEX; 2006	MTX, 16.4± 8.8 mg weekly	520	52.2±12.2	12.1±8.3	81	1.9±0.5	23.4±11.8	33.9±15.1	6.9±1.0	5
TOC Emery RADIATE 8 mg; 2008	MTX (15.7±4.4 mg)	499	53.9±12.7	12.6±9.3	84	1.7±0.6	18.9±10.9		7.0±0.9	3

*Mixed population of patients receiving MTX (75%), and patients receiving monotherapy.
†Subgroup of patients receiving a combination of GOL and MTX.
‡Numbers are mean±SD if not indicated otherwise.
§Median (IQR).
ABA, abatacept; DAS, Disease Activity Score; DMARD, disease modifying drugs; GOL, golimumab; HAQ-DI, Health Assessment Questionnaire-Disability Index; MTX, methotrexate; RTX, rituximab; SJC, swollen joint count; TJC, tender joint count; TOC, tocilizumab.

<u>Direct comparison:</u>
abatacept, golimumab, rituximab and tocilizumab vs. placebo:

- statistically significant mean ORs of 3.3-8.9 for ACR20, 5.5-10.2 for ACR50 and 4.1-13.5 for ACR70.
- Risks of AEs, SAEs and SIs vs. placebo were non-significant.

<u>Indirect pairwise comparisons</u>
Efficacy

- The four biological agents showed no significant differences in ACR50 and ACR70.
- Golimumab had a significantly lower OR (0.56-0.59) for ACR20 but significantly

fewer AEs (RD 0.13-0.18).

- Efficacy after one vs. multiple TNF inhibitors failures did not differ significantly between the different biological agents.

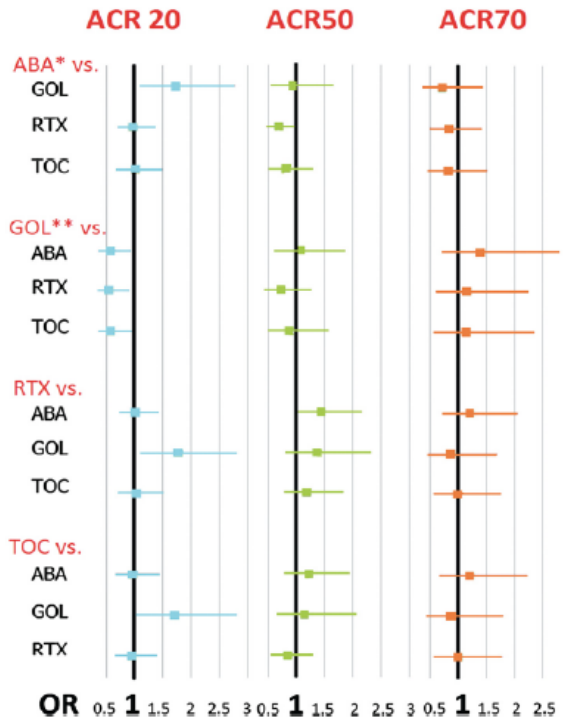


Figure 3 Efficacy in pairwise comparisons. similar success rates of abatacept (ABA), golimumab (GOL), rituximab (RTX), tocilizumab (TOC). Top to bottom: ABA is comparator versus GOL, RTX, TOC; GOL versus ABA, RTX, TOC; RTX versus ABA, GOL, TOC; TOC versus ABA, GOL, RTX. OR (95% CI) for American College of Rheumatology (ACR)20 (left column), ACR50 (middle column) and ACR70 (right column) are displayed in red. Black vertical lines indicate an OR of 1. ORs>1 (right of the black line) favour the comparator drug shown in red, ORs<1 (left of the black line) indicate poorer response rates than with the red comparator drug shown in red.

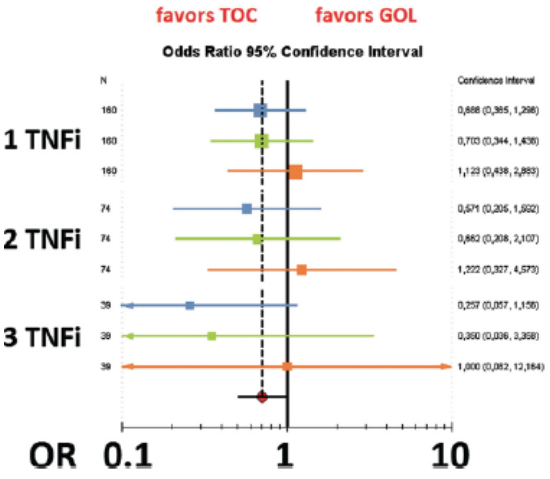


Figure 4 Efficacy after multiple tumour necrosis factor inhibitor (TNFi) failures. Response rates of golimumab (GOL) and tocilizumab (TOC). American College of Rheumatology (ACR)20 (blue lines), ACR50 (green lines) and ACR70 (orange lines) of patients for whom one (top), two (middle) and three (bottom) TNFi had previously failed.

Safety

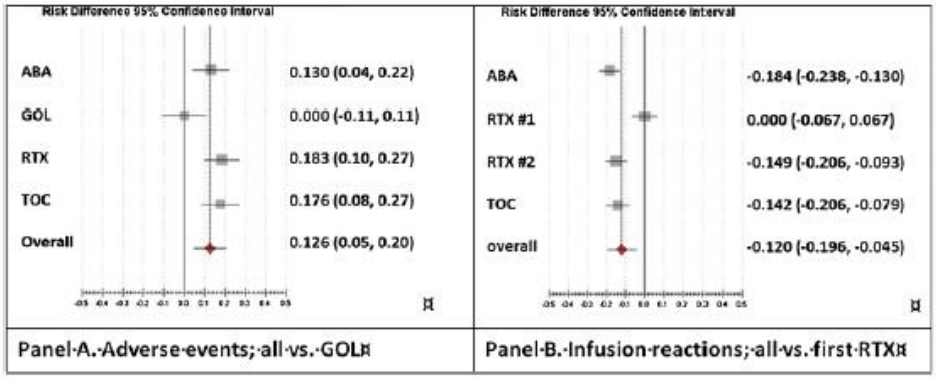
	 **Figure 5** Drug safety. (A) Pairwise indirect comparison against golimumab (GOL): abatacept (ABA), rituximab (RTX) and tocilizumab (TOC) show higher general adverse event rates. (B) Infusion reactions within 24 h: pairwise indirect comparison against the first RTX infusion (RTX #1) shows higher risk than in TOC and ABA. **4. Fazit der Autoren:** In patients refractory to one or more TNF inhibitors, new biological agents provide significant improvement with good safety. Lacking head-to-head trials, indirect meta-analysis enables a comparison of effectiveness and safety of biological agents with each other and shows that all biological agents have similar effects. In conclusion, in this patient group characterised by disease refractory to multiple previous treatments, significant improvement is possible with approved biological agents, which also show acceptable safety outcomes in the studied trial populations. **5. Hinweise der FB Med** nur 2 der eingeschlossenen Studien berichteten incomplete response
Malottki K et al., 2011 [28]. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a tumour necrosis factor inhibitor: a systematic review and economic evaluation	**1. Fragestellung** To assess the clinical effectiveness and cost-effectiveness of adalimumab, etanercept, infliximab, rituximab and abatacept when used in patients with RA who have tried conventional agents and have failed to improve after trying a first TNF inhibitor.
	2. Methodik ***Population:*** Patients with RA who have tried conventional agents and have failed to improve after trying a first TNF inhibitor ***Interventionen, Kontrolle (Vergleiche)***: Adalimumab (ADA), etanercept (ETN), infliximab (IFX), rituximab (RTX), abatacept (ABT) ***Endpunkt***: clinical outcomes related to efficacy, safety or tolerability treatment withdrawal (and reasons for withdrawal) ***Suchzeitraum (Aktualität der Recherche):*** Bis 2009 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 5 RCTs, 1 comparative study 1 controlled study 28 uncontrolled studies Weitere Einschlusskriterien: • mindestens 12 Wochen Studiendauer • for non-randomised studies – at least 20 patients in one arm
	3. Ergebnisdarstellung

TABLE 2 Mapping of identified studies

Comparators	Interventions (newly initiated)					
	ADA	ETN	IFX	TNF inhibitors	RTX	ABT
None[a]	Bennett 2005[92] (n = 26, 52 weeks) Wick 2005[93] (n = 27, 24 weeks) Nikas 2006[94] (n = 24, 52 weeks) Bombardieri 2007[95,96] (n = 899, 12 weeks) van der Bijl 2008[97] (n = 41, 16 weeks)	Haraoui 2004[98] (n = 25, 12 weeks) Buch 2005[99] (n = 207, 12 weeks) Cohen 2005[100] (n = 24, 13 weeks) Buch 2007[101] (n = 95, 12 weeks) Iannone 2007[102] (n = 37, 24 weeks) Laas 2008[103] (n = 49, >36 weeks) Bingham 2009[104] (n = 201, 16 weeks)	Ang 2003[105] (n = 24, unclear) Hansen 2004[106] (n = 20, unclear) Yazici 2004[107] (n = 21, unclear)	Gomez-Reino 2006[108] (n = 488, 104 weeks) Solau-Gervais 2006[109] (n = 70, > 13 weeks) Hjardem 2007[110] (n = 235, 13 weeks) Duftner 2008[111] (n = 109, up to 208 weeks) Karlsson 2008[112] (n = 337, 13 weeks) Blom 2009[113] (n = 197, 48 weeks)	Bokarewa 2007[114] (n = 48, 52 weeks) Jois 2007[115] (n = 20, 26 weeks)[b] Keystone 2007[116] (n = 158, 24 weeks) Assous 2008[117] (n = 50, 26 weeks) Thurlings 2008[118] (n = 30, 24 weeks)	ATTAIN LTE[119] (n = 317, < 260 weeks) ARRIVE[120] (n = 1,046, 24 weeks)

Quantity and quality of evidence: No directly relevant head-to-head trial directly comparing any of the five technologies against each other or directly comparing any of the technologies against other biologics or previously untried, newly initiated DMARDs, was found.

Comparative effectiveness: No RCT provided evidence on genuine head-to-head comparisons between the technologies, other biologics and newly initiated, previously untried DMARDs.

<u>Evidence from randomised controlled trials</u>

The effectiveness of RTX was demonstrated in a good-quality RCT (REFLEX). At 6 months, significantly more patients treated with RTX achieved American College of Rheumatology (ACR) 20 [relative risk (RR) = 2.85, 95% confidence interval (CI) 2.08 to 3.91] and ACR70 (RR = 12.14, 95% CI 2.96 to 49.86) compared with those treated with the placebo. Significant differences between groups in favour of RTX were observed at 6 months for mean change from baseline in Disease Activity Score 28 (DAS28) (mean difference –1.50, 95% CI –1.74 to –1.26) and mean change from baseline in Health

	Assessment Questionnaire (HAQ) score (mean difference –0.30, 95% CI –0.40 to –0.20). The effectiveness of ABT was demonstrated in a good-quality RCT (ATTAIN). At 6 months, significantly more patients treated with ABT achieved ACR20 (RR = 2.56, 95% CI 1.77 to 3.69) and ACR70 (RR = 6.70, 95% CI 1.62 to 27.80) compared with those treated with the placebo. Significant differences between groups in favour of ABT were observed at 6 months for mean change from baseline in DAS28 score (mean difference –1.27, 95% CI –1.62 to –0.93) and mean change from baseline in HAQ score (mean difference –0.34, insufficient data for calculating 95% CI). One small RCT (OPPOSITE, n = 27) compared switching to IFX versus staying on ETN in patients who had incomplete response to ETN. The study population was not well defined and the comparator was considered inappropriate for this assessment. Two additional RCTs evaluated concurrent use of ABT and TNF inhibitor, which is not recommended in its licence. These studies were not further assessed.
	4. **Fazit der Autoren:** Evidence from RCTs suggests that RTX and ABT are more effective than supportive care. Data from observational studies suggest that the use of an alternative TNF inhibitor in patients who exhibit an inadequate response to a first TNF inhibitor may offer some benefit, but there remain uncertainties with regard to the magnitude of treatment effects and their cost-effectiveness. Future research should include head-to-head trials comparing the clinical effectiveness and cost-effectiveness of the technologies against each other and emerging biologics. Limitations: Paucity of evidence from RCTs for assessing the clinical effectiveness of TNF inhibitors and an absence of head-to-head trials comparing the five technologies.
Kim HL et al., 2014 [20]. Comparative effectiveness of cycling of tumor necrosis factor-α (TNF-α) inhibitors versus switching to non-TNF biologics in rheumatoid arthritis patients with inadequate response to TNF-α inhibitor using a Bayesian approach.	**1. Fragestellung** The objective of this study was to use Bayesian approach to compare the effectiveness of cycling TNF- α inhibitors versus switching to non-TNF biologics in TNF-IR patients.
	2. Methodik ***Population:*** Patients with RA who failed to respond to previous treatments with TNF-α inhibitors. ***Intervention:*** Cycling TNF-α inhibitors (means: after failure of the initial TNF- α treatment, an alternative TNF-α inhibitor will be given) ***Kontrolle:*** Switching to non-TNF biologics (means: after failure of the initial TNF- α treatment, an non-TNF biologic will be given) ***Endpunkte:*** ACR response 20/50/70, HAQ score change at six months ***Suchzeitraum (Aktualität der Recherche):*** A systematic review was conducted using MEDLINE and Cochrane Library until 2013. ***Anzahl eingeschlossener Studien/Patienten (Gesamt):*** 6 studies ***Qualität der Studien:*** Quality assessment performed using the Cochrane's risk of Bias, but no final evaluation of the quality described in the review.
	3. Ergebnisdarstellung • one study of golimumab,

	• one study of rituximab, • two studies of abatacept, • two studies of tocilizumab. All studies were conducted in samples of patients who failed initial TNF-α treatment and baseline characteristics were similar across all studies; no or unclear risk of bias . <u>ACR response 20/50/70:</u> • The proportion of patients who achieved **ACR20** was highest for tocilizumab (62,4%), followed by rituximab (47%), abatacept (43,7%) and golimumab (32,1%) and lowest for placebo (15,5%). • Similarly, the ACR50 effectiveness measure was highest for tocilizumab and lowest for placebo. • Rituximab had the highest proportion of patients who achieved ACR70. • ORs for non-TNF biologics in comparison to golimumab, a TNF-alfa inhibitor shows: For ACR20, abatacept had an OR of 1,639 (95% Crl 0,786-3,408; P(OR> 1)= 90,7%), rituximab 1,871 (95% Crl 0,937-3,725; P(OR>1)=96,2%), and tocilizumab 3,52 (95% Crl 1,567-7,946; P(OR>1)=99,9%). • The posterior probabilities of all non-TNF biologics were over 90%, suggesting that these agents were more effective. • For **ACR50**, ORs were: 1,623 (95% Crl 0,454-6,247; P(OR> 1)= 72,2%), 1,702 (95% Crl 0,558-5,087; P(OR>1)=83%), and 2,552 (95% Crl 0,752-9,1; P(OR>1)=93,3%) for abatacept, rituximab and tocilizumab, respectively. • For **ACR70**, ORs were: 2,048 (95% Crl 0,361-16,47; P(OR> 1)= 78,4%), 3,876 (95% Crl 0,685-35,37; P(OR>1)=93,5%), and 3,107 (95% Crl 0,532-25,49; P(OR>1)=89,2%) for abatacept, rituximab and tocilizumab, respectively. In this case, rituximab was shown tob e more effective than the TNF-alfa inhibitor based on the probability of OR>1. <u>HAQ score change:</u> • The median differences were -0,259 for abatacept, -0,160 for rituximab, and -0,200 for tocilizumab. • The probability of being the best among five treatments was highest for abatacept at 74.4%. • Comparisons of each bDMARD with placebo showed that the magnitude of the change was the highest for abatacept, followed by tocilizumab and tiruximab, and lowest for folimumab. Based on the posterior probabilities, non TNF biologics improved HAQ scores compared with then TNF-alfa inhibitor.
	4. Fazit der Autoren: *Switching to non-TNF biologics was more effective than cycling TNF-alfa inhibitor in TNF-IR patients.* **5. Anmerkungen der Autoren/FBMed:** • Limited clinical evidence (only one RCT available for each variable) • Duration of the studies too short to assess long-term benefits (vs. RA is a chronic disease) No head-to-head studies available; results based on indirect evidence/comparison
Zhou Q et al., 2014 [47]. The efficacy	**1. Fragestellung** To assess the efficacy and safety of CZP in the treatment of RA patients
	2. Methodik

and safety of certolizumab pegol (CZP) in the treatment of active rheumatoid arthritis (RA): a meta-analysis from nine randomized controlled trials	**Population:** adult patients with RA I**ntervention**: CZP or CZP-based therapy (CZP+MTX) **Komparator**: placebo therapy (placebo or placebo+MTX) **Endpunkte:** ACR20, ACR50, ACR70, disease activity and PROs, and AEs **Suchzeitraum** (Aktualität der Recherche): up to June 14, 2014 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 9 (5228 patients) **Qualitätsbewertung der Studien:** Jadad scale.
	3. Ergebnisdarstellung • 3 trials with CZP vs placebo, • 6 trials with CZP plus MTX vs placebo+MTX • all of the nine studies had a high quality, and the median Jadad score was 4 (range from 4 to 5) *Results* • CZP (200 or 400 mg) combined with MTX associated with significantly higher ACR20, ACR50 and ACR70 response rates at week 12 and 24, and had amelioration in PROs, including HAQ-DI, arthritis pain, and fatigue, in the treatment of patients with active RA. • incidence of AEs (any intensity) between the CZP group and control group was not statistically significant difference
	4. Fazit der Autoren CZP 200 or 400 mg is clinically effective in the treatment of active RA patients. **5. Hinweise FBMed** • Keine Darstellung der Effektschätzer für CZP + MTX vs MTX, Effektschätzer nur über alle Studien angegeben • Studienpopulation: Patienten mit inadäquater Response gegenüber MTX bzw. DMARDs
Chen M et al., 2015 [6]. Efficacy of etanercept for treating the active rheumatoid arthritis: an updated meta-analysis	**1. Fragestellung** To evaluate the efficacy of etanercept (ETA) for treating active rheumatoid arthritis (RA) compared to placebo or methotrexate (MTX).
	2. Methodik **Population:** adult patients with RA I**ntervention**: Etanercept **Komparator** placebo or/and MTX **Endpunkte:** u.a. ACR20, ACR50 and ACR70 **Suchzeitraum** (Aktualität der Recherche): Bis 05/2014 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 12 (n= 3878) **Qualitätsbewertung der Studien:** Cochrane Risk of Bias .

	3. Ergebnisdarstellung • 6 Studies with ETA vs MTX • 3 Studies with ETA + MTX vs placebo+MTX (or usual DMARD+MTX) • 3 Studies with ETA vs Placebo <u>ETA (25 mg twice weekly) vs MTX: mean change in total Sharp Score within 1–3 years (4 studies)</u> The MD of mean change in Sharp Score at 1, 2, 3 years were -3.07 (95% CI: -5.72 to -0.42, P = 0.02), -2.24 (95% CI: -4.61 to 0.13, P = 0.06) and -4.34 (95% CI: -7.56 to -1.12, P = 0.008), respectively → superiority of ETA at 1 and 3 years
	4. Anmerkungen/Fazit der Autoren In active RA patients treated with ETA, there was significantly higher efficacy compared to the treatment of placebo or MTX. High doses of ETA were more effective for active RA patients **5. Hinweise durch FB Med** • ACR-Response-Effektschätzer nur für alle Studien zusammendargestellt (mit sig. Vorteil für ETA, hier nicht dargestellt), nicht differenziert nach den unterschiedlichen Vergleichen • Studienpopulation: sowohl Studien mit MTX-naiven Patienten als auch mit Patienten mit inadäquater Response ggü. MTX/DMARDs
Graudal N et al., 2014 [16] Effect of Combination Therapy on Joint Destruction in Rheumatoid Arthritis: A Network Meta-Analysis of Randomized Controlled Trials	**1. Fragestellung** Comparing combination treatment versus single DMARD treatment in RA
	2. Methodik Network Meta-analysis **Population:** patients with RA I**nterventionen**: combination treatments of • methotrexate plus TNF inhibitors (etanercept (Et),infliximab (In), adalimumab (Ad), certolizumab (Cz), and golimumab(Go)), • methotrexate plus abatacept (Ab), • methotrexate plustocilizumab (Tz), and • methotrexate plus CD20 inhibitors (rituximab (Rt), ocrelizumab (Oc)) **Komparator:** single DMARD **Endpunkte:** change in radiographic erosion score **Suchzeitraum** (Aktualität der Recherche): Bis 07/2012 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 38 **Qualitätsbewertung der Studien:** Cochrane Risk of Bias <u>Review protocol has been registered in PROSPERO.</u>
	3. Ergebnisdarstellung Definition of 6 combination treatments vs single DMARD for the network MA (including 1 trial with direct comparison between TNFi, double and triple DMARD, and 2 trials with

direct comparisons between double and triple DMARDs): siehe Abb.

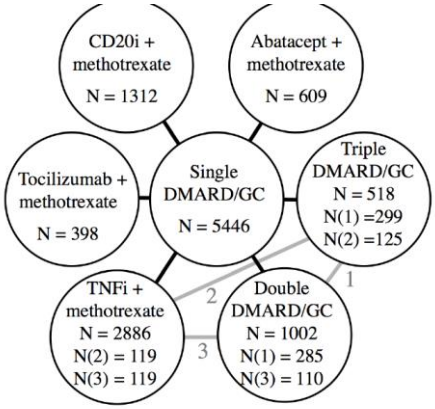
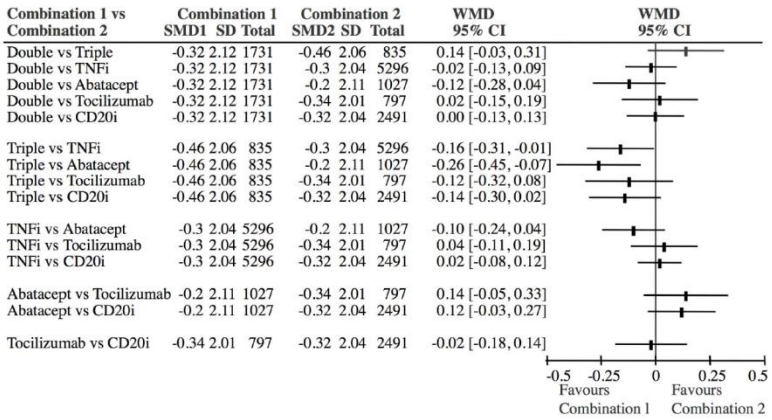


Figure 3. Star shaped network showing the 6 different combination treatments anchored on single treatment as the common comparator. The loops (grey lines) with corresponding numbers (1, 2, 3) show the subgroups, which were directly compared in addition to being indirectly compared. N indicates the number of patients in the groups.
doi:10.1371/journal.pone.0106408.g003

Results

The indirect comparisons showed similar effects between combination treatments apart from triple DMARD being significantly better than abatacept plus methotrexate (-0.26 SMD (CI: -0.45, -0.07)) and TNFi plus methotrexate (-0.16 SMD (CI: -0.31, -0.01)) (Figure 10)



Combination 1 vs Combination 2	Combination 1 SMD1	SD	Total	Combination 2 SMD2	SD	Total	WMD 95% CI
Double vs Triple	-0.32	2.12	1731	-0.46	2.06	835	0.14 [-0.03, 0.31]
Double vs TNFi	-0.32	2.12	1731	-0.3	2.04	5296	-0.02 [-0.13, 0.09]
Double vs Abatacept	-0.32	2.12	1731	-0.2	2.11	1027	-0.12 [-0.28, 0.04]
Double vs Tocilizumab	-0.32	2.12	1731	-0.34	2.01	797	0.02 [-0.15, 0.19]
Double vs CD20i	-0.32	2.12	1731	-0.32	2.04	2491	0.00 [-0.13, 0.13]
Triple vs TNFi	-0.46	2.06	835	-0.3	2.04	5296	-0.16 [-0.31, -0.01]
Triple vs Abatacept	-0.46	2.06	835	-0.2	2.11	1027	-0.26 [-0.45, -0.07]
Triple vs Tocilizumab	-0.46	2.06	835	-0.34	2.01	797	-0.12 [-0.32, 0.08]
Triple vs CD20i	-0.46	2.06	835	-0.32	2.04	2491	-0.14 [-0.30, 0.02]
TNFi vs Abatacept	-0.3	2.04	5296	-0.2	2.11	1027	-0.10 [-0.24, 0.04]
TNFi vs Tocilizumab	-0.3	2.04	5296	-0.34	2.01	797	0.04 [-0.11, 0.19]
TNFi vs CD20i	-0.3	2.04	5296	-0.32	2.04	2491	0.02 [-0.08, 0.12]
Abatacept vs Tocilizumab	-0.2	2.11	1027	-0.34	2.01	797	0.14 [-0.05, 0.33]
Abatacept vs CD20i	-0.2	2.11	1027	-0.32	2.04	2491	0.12 [-0.03, 0.27]
Tocilizumab vs CD20i	-0.34	2.01	797	-0.32	2.04	2491	-0.02 [-0.18, 0.14]

Figure 10. Indirect comparisons of different combination treatments. There is a trend towards triple treatment being superior to abatacept and TNFi. All other differences between the combination treatments are non-significant. Abbreviations: SMD: Standardized mean difference. WMD: Weighted mean difference (SMD1-SMD2).

Heterogeneity analysis of the study effects was insignificant indicating similar results from study to study and direct and indirect comparisons were consistent when comparing treatment balanced data

4. Anmerkungen/Fazit der Autoren

Combination treatment of a biologic agent with 1 DMARD is not superior to 2–3 DMARDs including or excluding LDGC in preventing structural joint damage. Future randomized studies of biologic agents should be compared versus a combination of DMARDs.

5. Hinweise FBMed

Studienpopulation: Studien mit Patienten mit inadäquater Response ggü. DMARDs als

	auch ohne DMARD-IR
Graudal N et al., 2015 [15] Combination therapy with and without tumor-necrosis factor inhibitors in rheumatoid arthritis.	**1. Fragestellung** To compared the effects of combination DMARD therapies with and without biologic agents as therapy for patients with rheumatoid arthritis.
	2. Methodik **Population:** patients with RA I**ntervention**: combinations of different DMARDs **Komparator** TNF-alpha-inhibitors + DMARDs **Endpunkte:** • ACR20, ACR50 and ACR70 • Joint radiograph scores • disease activity score 28 (DAS28) • health assessment questionnaire (HAQ) scores **Suchzeitraum** (Aktualität der Recherche): Bis 09/2014 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 8 (n= 3878) **Qualitätsbewertung der Studien:** Cochrane Risk of Bias Review protocol has been registered in PROSPERO.
	3. Ergebnisdarstellung • infliximab and etanercept (combined with MTX) were identified as biologic drugs being compared with combinations of DMARDs • 3 studies with DMARD naïve patients; 5 studies with patients with inadequate response to DMARD *Results* • Change in joint radiographic progression score did not differ between the combination DMARD group and the TNFi group, neither during the second year (MD -0.09 [-0.61,0.44]) of treatment nor during the first two years (MD 0.66 [-0.12, 1.43]). • At 6 months, there were significant differences in radiographic progression score (MD 0.49 [0.15; 0.83]), ACR50 (RR 1.44 [1.01; 2.06]) and ACR70 (RR 1.90 [1.27;2.85]) in favor of TNFi but these differences were not present in patients treated with an initial steroid course and disappeared at 24 months irrespective of the use of steroids. • There was no difference in number of AEs. • Higher risk for drop-outs in the DMARD group than in the TNFi group (RR 1.47 [1.11;1.96])
	4. Anmerkungen/Fazit der Autoren The difference between DMARD combination treatments including or excluding TNF inhibitors is small. Due to the enormous cost-differences RA guidelines should recommend combination DMARD treatment before initiation of TNF inhibitors **5. Hinweise durch FB Med** • Ergebnisse nicht stratifiziert nach DMARD-Vorbehandlungsstatus dargestellt

De Oliveira Costa J et al., 2015 [8]. Infliximab, methotrexate and their combination for the treatment of rheumatoid arthritis: a systematic review and meta-analysis	**1. Fragestellung** To evaluate the efficacy and safety of infliximab + methotrexate (IFX + MTX) regimens versus MTX alone or in combination with other disease-modifying anti-rheumatic drugs (DMARDs).
	2. Methodik **Population:** RA patients regardless of disease duration **Intervention** IFX + MTX **Komparator** MTX as monotherapy or in combination with other synthetic DMARD **Endpunkt:** ACR20,ACR50, ACR70, clinical remission defined as DAS28, Patient's assessment of physical function **Suchzeitraum** (Aktualität der Recherche): until June/October 2012 **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 9 **Qualitätsbewertung der Studien:** Jadad score and Cochrane Risk of Bias
	3. Ergebnisdarstellung *Study characteristics* Patients profile included individuals previously treated with DMARDs, not treated with MTX (2 studies) or those that had insufficient responses to MTX. *Methodological quality and risk of bias* Nine trials were classified as randomised, but only two of these studies reported the methods of randomisation. The Jadad scale score was generally good (ranging from moderate to high). The pharmaceutical industry funded six studies. We identified a potential source of bias in three trials, and only one study was classified as low risk of bias *Efficacy of infliximab vs control* Patients with insufficient response to MTX (6 studies): ACR20: RR1.77 (1.38 to 2.62); I2=74% ACR50: RR 2.13 (1.53; 2.97); I2=61% ACR70:RR 2.18 (1.43; 3.34, I2=43% MTX-naïve Patients (2 Studies) ACR20: RR 1.40 (0.84; 2.34); I2=64% ACR50: RR 1.44 (1.18; 1.76); I2=0% ACR70: RR 1.56 (1.19; 2.04); I2=0% *Safety* • no statistically significant differences between the IFX standard dose + MTX and DMARDgroups in the outcomes of infection, serious infections, serious adverse events, tumours and death. • Infusion reactions occurred more frequently in the IFX + MTX group (RR = 2.21[1.63; 2.99]) • serious infections and infusion reactions showed moderate heterogeneity.

	• Subgroup analysis revealed that MTX-naive patients who received IFX + MTX had more serious infections than the MTX group (2.80 [1.14; 6.84], 1 Study)
	4. Fazit The IFX + MTX combination is more effective than treatment with MTX alone or DMARDs combination. The IFX + MTX regimen presented good tolerability in patients previously treated with DMARDs, not treated with MTX or with insufficient responses to MTX. The efficacy of IFX + MTX is noted primarily during initial periods of treatment. High doses of IFX were as effective as the standard dose, but with possible higher risk of serious infections
Barra L et al., 2014 [2]. Efficacy of biologic agents in improving the Health Assessment Questionnaire (HAQ) score in established and early rheumatoid arthritis: a meta-analysis with indirect comparisons	**1. Fragestellung** To determine the comparative efficacy of biologic agents in improving HAQ in patients with established RA who failed DMARDs or anti-TNF agents and in early RA (ERA).
	2. Methodik MA + indirect comparison **Population:** patients > 15 years with RA; differentiation between: • (i) established RA patients failing DMARDs or • (ii) established RA patients failing anti-TNF at enrolment and • (iii) patients with ERA (as symptoms <2 years or <10% prior exposure to a biologic agent,) I**nterventionen**: biologics for RA **Komparator:** single DMARD **Endpunkte:** improvement in HAQ **Suchzeitraum** (Aktualität der Recherche): Bis 08/2012 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 28 **Qualitätsbewertung der Studien:** Jadad score Indirect comparisons of the different drugs compared to the control group were conducted using the Q-test based on analysis of variance and reported as a p-value (p-value <0.05 was considered significant).
	3. Ergebnisdarstellung • 28 studies: ○ 17 trials on anti-TNF agents (7 adalimumab, 3 certolizumab, 4 etanercept,1 golimumab and 2 infliximab), ○ 4 trials on abatacept, ○ 3 trials on rituximab and ○ 4 trials on tocilizumab. • *Quality assessment:* jadad score of 4 trials = 3 (poor quality); majority of trials (n=19) had >20% cross-over from the control group to intervention groups and these studies used intention-to-treat analyses. *Efficacy of biologic agents at lowering HAQ in established RA patients failing DMARDs (19 studies,, n=8115)*

	• analysis of the different biologics revealed a significant difference in mean difference in change in HAQ (p<0.0001). ○ The $\Delta HAQ_{biologic}$-$\Delta HAQ_{control}$ for abatacept (-0.20; 95% CI:-0.28, -0.12; I2=0%), and infliximab (-0.11; 95% CI: -0.17, -0.05; I2=0%) were significantly lower than the other anti-TNF agents with $\Delta HAQ_{biologic}$-$\Delta HAQ_{control}$ of -0.32 to -0.35; I2=0% for all) (p<0.02) ○ $\Delta HAQ_{biologic}$-$\Delta HAQ_{control}$ for tocilizumab (-0.20; 95% CI:-0.24, -0.17; I2=0%) was lower compared to adalimumab and certolizumab (p<0.001) *Efficacy of biologic agents at lowering HAQ in established RA patients failing anti-TNF agents (4 studies, n=1694)* There were no significant differences in the efficacy of the different biologics at improving HAQ: $\Delta HAQ_{biologic}$-$\Delta HAQ_{control}$ was for • abatacept of -0.40; 95% CI:-0.51, -0.29), • rituximab (-0.37; 95% CI: -0.46, -0.27) and • tocilizumab (-0.36; 95% CI:-0.42, -0.30). *Efficacy of biologic agents at lowering HAQ in early RA (ERA) patients (5 studies, n=2492).* • 1 trial investigating infliximab with DMARD-naïve patients • 4 trials with MTX-naïve patients (subjects could have been exposed to other DMARDs previously There was no significant difference in HAQ improvement for the different biologic agents. The $\Delta HAQ_{biologic}$-$\Delta HAQ_{control}$ was for • adalimumab -0.20; 95%CI: -0.34, -0.06; • etanercept -0.3; 95%CI: -0.52, -0.07; • infliximab -0.2; 95%CI: -0.40, 0; and • rituximab -0.23; 95%CI: -0.32, -0.14)
	4. Fazit der Autoren Biologics improve physical function in established RA patients failing DMARDs and anti-TNF agents. In anti-TNF failures, the included biologics (abatacept, tocilizumab and rituximab) appeared equally efficacious. In DMARD-failures, there were differences in HAQ reduction for some biologics. These differences should be interpreted in the context of the doses used, the populations studied and the design of the included studies. **5. Hinweise FBMed** • Keine Informationen, welche Kontrollen in den Studien eingesetzt wurden
Kourbeti IS et al., 2014 [21]. Biologic Therapies in Rheumatoid Arthritis and the Risk of Opportunistic Infections: A Meta-analysis	**1. Fragestellung** We aimed to review their association with opportunistic infections (OIs), including fungal, viral (with a focus on herpes virus related infections), tuberculosis and other mycobacterial infections.
	2. Methodik ***Population:*** Patients with RA ***Intervention:*** Any approved biologic agent ***Kontrolle:*** Included either placebo or disease-modifying antirheumatic drugs/conventional therapy)

	Hinweis: Low-dose corticosteroids (<10 mg equivalent to prednisolone) were permitted in all arms. ***Endpunkte:*** Opportunistic Infections (OIs) including fungal, viral (with a focus on herpesvirusrelated infections), tuberculosis and other mycobacterial infections ***Suchzeitraum (Aktualität der Recherche):*** We searched PubMed and EMBASE through June 24, 2013, and complemented the search with the reference lists of eligible articles. The analysis included randomized trials on RA that compared any approved biologic agent with controls and reported the risk of OIs. ***Anzahl eingeschlossener Studien/Patienten (Gesamt):*** 70 ***Qualitätsbewertung der Studien:*** GRADE approach
	3. Ergebnisdarstellung A total of 70 trials that included 32 504 patients (21 916 patients receiving biologic agents and 10 588 receiving placebo) included → Studies of patients with prior TNF exposure = 8! *Study quality* The majority of studies were considered high quality based on the criteria detailed in the methods section. More specifically, across eligible studies, 68 of 70 (97%) were doubleblinded, 62 of 70 (89%) included intention-to-treat analysis, 68 of 70 (97%) reported dropouts, and 67 of 70 (96%) provided institutional review board approval and informed consent. Most trials (67 of 70; 96%) were multicenter; allocation concealment was provided in 23 of 70 studies (33%) and was unclear in 47 (67%). *Summary of effects* • There was high quality of evidence that biologic agents are associated within increased risk of all OIs: patients receiving biologic agents were more likely to develop OIs than control patients (OR, 1.79; 95% CI, 1.17–2.74) • use of biologic agents was associated with increased risk of mycobacterial infections (OR, 3.73; 95% CI, 1.72–8.13;I2 = 0) and all viral OIs (OR, 1.91; 95% CI, 1.02–3.58; I2 = 0), • no stat. sig.differences for all fungal infections (OR, 1.31; 95% CI, 0.46–3.72), invasive fungal infections (OR, 2.85; 95% CI, 0.68– 11.91), P. jirovecii pneumonia (OR, 1.77; 95% CI, 0.42–7.47), and VZV infections (OR, 1.51; 95% CI, 0.71–3.22), • combined effect of anti-TNF drugs was significant for OIs (OR, 2.10; 95% CI, 1.27–3.45; I2 = 0), as opposed to non–anti-TNF agents (OR, 1.20; 95% CI, .54–2.68); this comparison of effects was not significant (P interaction= 0.18). • A difference that did not reach statistical significance was noted for patients without prior exposure to anti-TNF agents (OR, 2.05; 95% CI, 1.23–3.42; I2 = 0) compared with those with previous exposure to anti-TNF agents (OR, 1.33; 95% CI, 0.62–2.85; I^2= 31%; P interaction = .36). • There was no difference in OI-associated mortality
	4. Fazit der Autoren: Among patients with RA, biologic agents are associated with a small but significant risk of specific OIs. This increase is associated with mycobacterial diseases and does not seem to affect overall mortality. Because OIs are a relatively rare complication of biologic agents, large registries are needed to identify the exact effect in different OIs

	and to compare the different biologic agents
Singh JA et al., 2015 [40]. Risk of serious infection in biological treatment of patients with rheumatoid arthritis: a systematic review and meta-analysis	**1. Fragestellung** To compare the risk of serious infections in rheumatoid arthritis between biological treatment and non-biological traditional treatment with DMARDs, and use network meta-analysis to compare subpopulations within rheumatoid arthritis, to synthesise data from RCTs
	2. Methodik Systematic review, meta-analysis, and Bayesian network meta-analysis **Population:** RA patients I**ntervention**: biologics **Komparator** placebo, biologics, or traditional DMARDs or their combinations **Endpunkte:** malignancies **Suchzeitraum** (Aktualität der Recherche): 02/2014 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 106 (n=42330) **Qualitätsbewertung der Studien:** Cochrane Risk of Bias Tool
	3. Ergebnisdarstellung • Risk of bias ranged from low to high across the studies • results stratified by the following populations: (siehe Tab.1) ○ MTX-naïve (24 trials), ○ traditional DMARD-experienced (71 trials), and ○ anti-TNF biological drug-experienced (11 trials) pts

	All populations	Traditional DMARD-naive patients	Traditional DMARD-experienced patients	TNF-experienced patients
Number of trials	106 (100%)	24 (23%)	71 (67%)	11 (10%)
Number of patients in trials	42 330 (100%)	8375 (20%)	29 167 (69%)	4788 (11%)
Number of patients with serious infection	965 (100%)	227 (24%)	646 (67%)	92 (10%)
Median year of publication	2008 (1992–2013)	2006 (1992–2013)	2008 (1994–2013)	2008 (2005–2013)
Number of treatment nodes	10	5	10	6
Number of two-arm trials	63 (100%)	19 (30%)	38 (60%)	6 (10%)
Number of multi-arm trials	43 (100%)	5 (12%)	33 (77%)	5 (12%)
Mean follow-up duration (months)	9·0 (8·0, 1–60)	13·1 (6·9, 3–24)	8·0 (8·5, 1–60)	6·3 (3·2, 2–12)
Number of trials with duration ≥12 months	33 (31%)	17 (71%)	18 (25%)	2 (18%)
Mean rheumatoid arthritis duration (years)	6·9 (4·0, 0·1–13·5)	0·7 (0·7, 0·1–3·5)	8·5 (2·3, 2·2–13·5)	10·8 (2·0, 6·4–12·9)
Mean annualised baseline risk of serious infection in traditional DMARDs arms*	2% (2, 0–9%)	2% (2, 0–9%)	2% (2, 0–8%)	2% (2, 0–5%)

Data are n (%), year (range), mean (SD, range), or % (range). TNF=tumour necrosis factor. *Only included trials more than 6 months in duration for calculation. DMARD=disease-modifying antirheumatic drugs.

Table: Characteristics of patients and studies

Serious infections

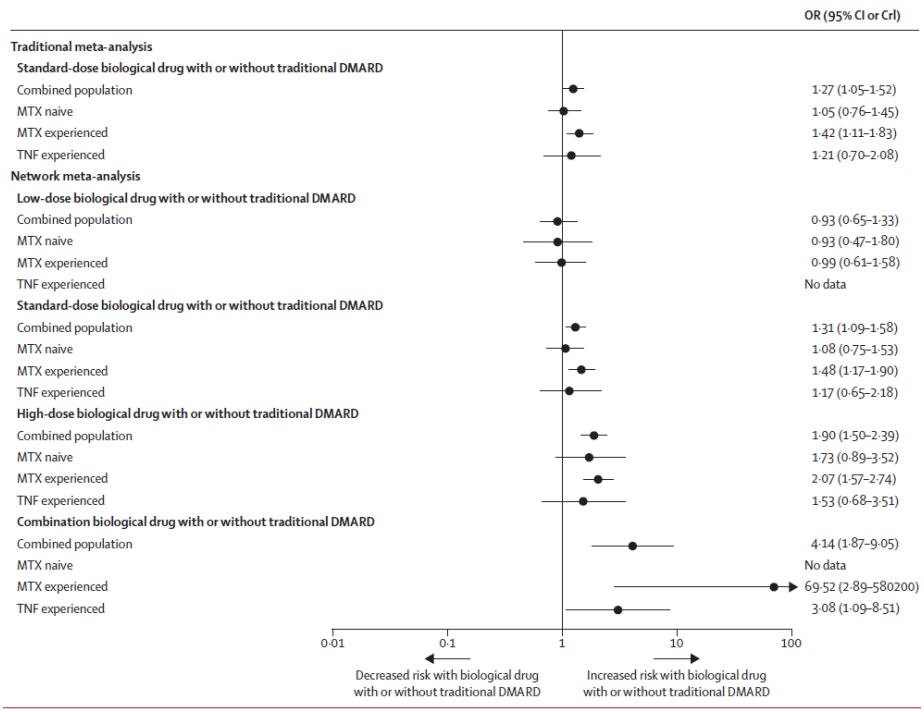


Figure 3: **Traditional meta-analysis and network meta-analysis**
Risk of serious infection among specified populations of patients compared with patients receiving traditional DMARD monotherapy. Data for the traditional meta-analysis are OR (95% CI) and data for the network meta-analysis are OR (95% CrI). OR=odds ratio. CrI=credible interval. DMARD=disease-modifying antirheumatic drugs.

Traditional Meta-analysis: (siehe Figure 3)

- significant increase in serious infections in patients receiving biological drugs (OR 1·27, 95% CI1·05–1·52, p=0·012
- risk of serious infections in patients treated with biological drugs varied depending on previous treatment experience
    - risk was significantly increased in MTX-experienced patients,
    - risk did not significantly differ in patients who were MTXnaive or anti-TNF-biological drug experienced

Network MA: (siehe Figure 3)

- standard-dose and high-dose biological drugs with or without traditional DMARD were associated with an increased risk of serious infection, low dose were not.
- In MTX-naïve patients, standard-dose biological drugs with or without traditional DMARD and high-dose biological drugs with or without traditional DMARD were not associated with a significant increase in risk of serious infection
- in MTX-experienced patients, standard-dose biological drugs with or without traditional DMARD and high-dose biological drugs with or without traditional DMARD were associated with an increased risk of serious infections.

In MTX-experienced and anti-TNF biological drug experienced patients combination biological significantly increase serious with wider CI

4. Fazit der Autoren

Standard-dose and high-dose biological drugs (with or without traditional DMARDs) are associated with an increase in serious infections in rheumatoid arthritis compared with traditional DMARDs, although low-dose biological drugs are not.

Liu Y et al., 2014 [25].

Risk of Breast Cancer and

1. Fragestellung

To analyze the risk of malignancies, especially breast cancer, in patients with RA enrolled in RCTs

2. Methodik

Total Malignancies in Rheumatoid Arthritis Patients Undergoing TNF-α Antagonist Therapy: a Meta-analysis of Randomized Control Trials	**Population:** adult RA patients I**ntervention**: TNF-α antagonists (orTNF-α antagonists plus MTX) **Komparator** placebo /MTX (or placebo plus MTX) **Endpunkte:** malignancies **Suchzeitraum** (Aktualität der Recherche): 07/2013 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 28 (n=11741) **Qualitätsbewertung der Studien:** Jadad scale
	3. Ergebnisdarstellung • Etanercept: 6 trials, • Infliximab: 5 trials, • certolizumab pegol: 4 trials, • adalimumab: 8 trials, • golimumab: 5 trials 71 malignancies were developed on TNF-α antagonists and 26 on placebo, and breast cancer was 10 *vs* 7. • No stat. sig. difference between groups for breast cancer (OR 0.65, 95%CI [0.22, 1.93] and for total malignancies (1.06, 95% CI 0.64, 1.75) • There were no significant differences among the five drugs at approved doses about risk of malignancies.
	4. Fazit der Autoren This study did not find a significantly increased risk of breast cancer and total malignancies in adults RA patients treated with TNF-α antagonists at approved doses. However, it cannot be ignored that more patients developed malignancies with TNF-α antagonists therapy compared with patients with placebo or MTX, in spite of the lack of statistical significance, so that more strict clinical trials and long-term follow-up are needed, and both mITT and PP analyses should be used in such safety analyses.
Michaud TL et al., 2014 [29]. The Comparative Safety of Tumor Necrosis Factor Inhibitors in Rheumatoid Arthritis: A Meta-analysis	**1. Fragestellung** to evaluate and update the safety data from RCTs of TNF inhibitors in patients treated for rheumatoid arthritis
	2. Methodik **Population:** > 18 year old RA patients I**ntervention**: TNF-α antagonists (adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab) **Komparator** placebo or DMARDs **Endpunkte:** • serious adverse events (any AE that resulted in death, was life threatening, resulted in hospitalization or prolongation of hospitalization, or caused persistent or substantial disability) • serious infection

Update of 44 Trials	• malignancies **Suchzeitraum** (Aktualität der Recherche): 05/2013 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 44 (n= 11700) **Qualitätsbewertung der Studien:** Cochrane risk of bias, GRADE
	3. Ergebnisdarstellung ○ Etanercept: 12 trials, ○ Infliximab: 9 trials, ○ certolizumab pegol: 5 trials, ○ adalimumab: 11 trials, ○ golimumab: 7 trials Quality of evidence: moderate to high *Results:* • Overall serious AE: no sign. difference (OR, 1.11; 95% CI, 0.97-1.26). ○ The results were consistent across trials (I2 <50%) for all drugs except etanercept (I2 =64.8%) • Malignancy: no sign. difference (OR, 1.29; 95% CI, 0.85-1.97) • Serious Infection: higher risk with TNFi (OR, 1.42; 95% CI, 1.13-1.78) ○ adalimumab: OR 1.69, 95% CI 1.12-2.54 →sig. difference ○ certolizumab pegol: OR 1.98, 95%CI 0.99-3.96 → n.s. ○ infliximab: OR 1.63, 95%CI 1.07-2.47 →sig. difference ○ golimumab OR 1.55, 95% CI 0.76-3.17 → n.s. ○ etanercept: OR 0.73; 95% CI 0.45-1.20 → n.s. • treatment discontinuation due to AE: higher risk with TNFi (OR, 1.23; 95% CI, 1.06-1.43) ○ adalimumab: OR 1.38, 95%CI 1.00; 1.69 →sig. difference ○ certolizumab pegol: 1.67, 95%CI 1.09; 2.54 →sig. difference ○ infliximab 2.04, 95%CI 1.46; 2.84 →sig. difference ○ etanercept: decreased risk of discontinuation due to AE (OR, 0.72; 95% CI 0.55-0.93) →sig. difference ○ golimumab OR 1.43, 95%CI 0.88; 2.35 →n.s. • infliximab plus MTX was associated with a significantly increased risk of serious infection compared with the MTX (OR, 1.63; 95% CI, 1.08-2.48).
	4. Fazit der Autoren There is higher risk of serious infection associated with adalimumab, certolizumab pegol, and infliximab, which seems to contribute to higher rates of discontinuation. In contrast, etanercept use showed a lower rate of discontinuation. **5. Hinweise FBMed** siehe auch Anlage 2:Übersicht der Ergebnisse bisheriger MA zur Sicherheit von TNF
Poiroux L et al., 2015 [35].	**1. Fragestellung** To compare mortality data obtained from RCTs for the 5 TNF-a inhibitors used in the

All-cause Mortality Associated with TNF-a Inhibitors in Rheumatoid Arthritis: A Meta-Analysis of Randomized Controlled Trials	treatment of rheumatoid arthritis.
	2. Methodik **Population:** adult RA patients I**ntervention**: TNF-α antagonists (adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab) **Komparator** placebo or DMARDs **Endpunkte:** all-cause mortality **Suchzeitraum** (Aktualität der Recherche): bis 10/2014 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 23 (n= 10048) **Qualitätsbewertung der Studien:** Jadad scale
	3. Ergebnisdarstellung • median study duration was 46 weeks (range: 24 to 104 weeks) • Most comparison analyses reached a high level of quality of evidence, with a mean Jadad score of 3.8±1.01 • risk of death with TNF-a inhibitors was not significantly different compared to control (OR]1.32; 95% CI 0.76-2.29), no differences between different TNFi • results were consistent across trials (P=0.99, I2 < 25%); type of comparator did not modify results; monotherapy and combination therapy
	4. Fazit der Autoren Treatment with TNF-a inhibitors is not associated with a higher risk of medium-term mortality of any cause in patients with rheumatoid arthritis. Further studies are warranted to assess the long-term effect of TNF-a inhibitors on mortality
Conway R et al., 2016 [7]. Leflunomide Use and Risk of Lung Disease in Rheumatoid Arthritis: A Systematic Literature Review and Metaanalysis	**1. Fragestellung** To evaluate the relative risk (RR) of pulmonary disease among patients with rheumatoid arthritis (RA) treated with leflunomide (LEF).
	2. Methodik Population: Adults with RA Intervention: LEF Komparator: not receiving LEF Endpunkt: respiratory side effects Suchzeitraum (Aktualität der Recherche): to April 15, 2014

of Randomized Controlled Trials	Anzahl eingeschlossene Studien/Patienten (Gesamt): Eight articles met the inclusion criteria and were included in our metaanalysis. The 8 articles reported on a total of 4579 patients, 2274 who received LEF and 2305 who received comparator treatments. Three studies involved synthetic disease-modifying antirheumatic drug (DMARD) comparators alone, 2 studies placebo comparators only, 2 placebo and synthetic DMARD comparator groups, and 1 paeoniflorin plus cervus and cucumis polypeptide injection. Qualität der Studien: Cochrane risk of bias tool.
	3. Ergebnisdarstellung Qualität der Studien: In general, the data suggested a low risk of bias in the included studies • There were 708 documented respiratory adverse events. LEF was not associated with an increased risk of total adverse respiratory events relative to comparator agents • LEF was not associated with an increased risk of infectious adverse respiratory events • LEF was associated with a decreased risk of noninfectious respiratory adverse events (RR 0.64, 95% CI 0.41–0.97, I2 = 0%) • There were 6 reported cases of pneumonitis, all in patients treated with MTX in the comparator group (not stat. significant) There were 4 pulmonary deaths, all in patients treated with MTX in the comparator group (not stat. significant).
	4. Fazit der Autoren: *The results of our metaanalysis demonstrate no increase in respiratory adverse events in patients with RA treated with LEF in double-blind RCT. Studies of pulmonary adverse events in patients treated with LEF and related agents for other diseases may provide further valuable information.*
Canadian Agency for Drugs and Technologies in Health (CADTH), 2013 [4]. Biologic Response Modifier Agents as First-line Treatment for Patients with Rheumatoid Arthritis: A Review of the Clinical Efficacy,	1. Fragestellung • What is the clinical efficacy of using biologics as first-line therapy in the treatment of patients with rheumatoid arthritis? • Are evidence-based clinical practice guidelines recommending biologic response modifier agents as first-line therapy?
	2. Methodik Population: MTX-naïve or traditional DMARD naïve patients with: -early RA or established RA, any severity of disease (mild-severe) Intervention: Biologic response modifier agents as first-line therapy (with or without combination MTX or DMARD): abatacept, adalimumab, anakinra, certolizumab, etanercept, golimumab, infliximab, rituximab, tocilizumab Komparator: MTX or traditional DMARD, combination DMARD therapy, placebo; Biologic vs. biologic Endpunkt: Clinical efficacy, safety, harms, cost-effectiveness, clinical practice guideline

Cost-effectiveness and Guidelines	recommendations Suchzeitraum (Aktualität der Recherche): up to 02/2013 Anzahl eingeschlossene Studien/Patienten (Gesamt): Qualität der Studien: Critical Appraisal of Literature (risk of bias,AGREE)
	3. Ergebnisdarstellung • First line treatment with biologic antirheumatic drugs in adults with rheumatoid arthritis (RA) was evaluated in 17 randomized controlled trials (RCTs) of moderate to good quality, published between 2000 and 2012. The biologic agents evaluated included adalimumab (5 RCTs), etanercept (3), golimumab (1), infliximab (5), abatacept (1), rituximab (1) and tocilizumab (1).Data from one RCT on rituximab (Tak 2009) was obtained from an abstract. No RCTs were identified that evaluated the efficacy of certolizumab or anakinra in RA patients who were MTX or DMARD naïve. • MTX or disease modifying antirheumatic drug (DMARD) naïve patients who received a biologic agent plus MTX were more likely to show a clinical improvement that met the American College of Rheumatology (ACR) 20, 50 or 70 criteria at six to 12 months, compared to those who received MTX alone. • Patients on biologic agents plus MTX were more likely to achieve clinical remission versus MTX alone, based on pooled data from seven RCTs, however studies published more recently have not shown a consistent advantage to early biologic therapy. • Most studies found that radiographic progression was less likely to occur for patients treated with biologic agents compared to DMARDs, although interpretation of these findings was difficult due to differences in how progression was defined. • The impact of first line biologic therapy on health related quality of life and work related outcomes were not consistent, and no conclusions can be drawn on the safety of biologic agents based on the data available. • The recommendations from evidence-based guidelines were inconsistent on the use of biologics in RA patients who were DMARD naïve. Three guidelines from Canada, US and Europe recommended that TNF inhibitors may be used as first line mono- or combination therapy in early RA patients (defined as disease duration ≤ 6 months) who are DMARD naïve and have poor prognostic factors, high disease activity, or have structural damage. One guideline from Scotland recommended against the use of TNF inhibitors in adults not previously treated with DMARDs. Anmerkung FBMed: EULAR-LL wurde in der Zwischenzeit aktualisiert: Deletion of former recommendation No 14: 'DMARD-naïve patients with poor prognostic markers might be considered for combination therapy of MTX plus a biological'. In 2010 it was already stated that early use of a biological agent should only be considered in exceptional patients; however, as it stood, this statement could have been misinterpreted as advocating use of biological agents even before an initial csDMARD strategy had failed. With the current decision, the use of bDMARDs before trying a csDMARD approach is even more strongly discouraged than signified by the 2010 recommendation. The majority of the current Committee members felt that using a treat-to-target strategy that gave patients the initial opportunity to respond to treatment in line with items 4, 5 and 7 still provides the option of adding a biological agent within 6 months—and thus quite early in the disease course or therapeutic chronology—if the treatment target was not reached

	4. Fazit der Autoren: ---

Leitlinien

Smolen JS et al., 2014 [45]. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update	European League against Rheumatism (EULAR) **Fragestellung** Updating the 2010 EULAR recommendations for the management of RA.
	Methodik evidenz- und interdisziplinär (Rheumatologie, Patientenvertretung, Gesundheitsökonomie, Infektiologie) konsentierte Leitlinie ***Grundlage der Leitlinie****:* 4 systematische Übersichtsarbeiten und (teilanonym.) Konsensus-prozesse[2] ***Suchzeitraum:*** zu 1. „up to January 2009“, zu 2. “from 1962 to February 2009“, zu 3. “between 1962 and February 2009“, zu 4. „until January 2013“ ***Weitere Kriterien für die Qualität einer Leitlinie:*** Quellen im jeweiligen Hintergrundtext zu den Empfehlungen zitiert ***LoE/GoR****:* LoE and GoR are based on the recommendations of the Oxford Centre for Evidence-Based Medicine SoR=level of agreement (scale 0 to 10 with 0=no agreement at all; 10=full agreement), %=percent of votes for the respective items as worded ***Sonstige methodische Hinweise:*** • Competing interests: All participants have disclosed any conflicts of interest. After review by the EULAR Steering Committee, these potential conflicts have been considered as either absent or accept-able with this initiative. The individual declarations of conflicts are available on demand at the EULAR secretariat and are summarised below as remuneration for consultation and/or speaking engagements (‘R’), research funding (‘F’) or ‘none’. Funding: EULAR
	Empfehlungen • MTX should be part of the first treatment strategy in patients with active RA.(LoE 1a, GoR A, SoR 9.6±0.9, 100%)

[2]Gaujoux-Viala C et al. Efficacy of conventional synthetic disease-modifying antirheumatic drugs, glucocorticoids and tofacitinib—a systematic literature review informing the 2013 update of the EULAR recommendations for management of rheumatoid arthritis. Ann Rheum Dis 2014;73:510–15.

Ramiro S, Gaujoux-Viala C, Nam JL, et al. Safety of synthetic and biological DMARDs—a systematic literature review informing the 2013 update of the EULAR recommendations for management of rheumatoid arthritis. Ann Rheum Dis 2013;73:529-35.

Nam JL, et al. Current evidence for the management of rheumatoid arthritis with biological disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of RA. Ann Rheum Dis 2010;69:976–86.

Gorter SL, et al. Current evidence for the management of rheumatoid arthritis with glucocorticoids: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis 2010;69: 1010–14.

	• In cases of MTX contraindications (or early intolerance), sulfasalazine or leflunomide should be considered as part of the (first) treatment strategy. (LoE 1a, GoR A, SoR 9.0±1.7, 87%) • In DMARD-naive patients, irrespective of the addition of glucocorticoids, csDMARD monotherapy or combination therapy of csDMARDs should be used. (LoE 1a, GoR A, SoR 9.5±0.8, 100%) • If the treatment target is not achieved with the first DMARD strategy, in the absence of poor prognostic factors, change to another csDMARD strategy should be considered; when poor prognostic factors are present, addition of a bDMARD should be considered. (LoE 5, GoR D, SoR 8.9±1.3, 100%) • In patients responding insufficiently to MTX and/or other csDMARD strategies, with or without glucocorticoids, bDMARDs (TNF inhibitors*, abatacept or tocilizumab, and, under certain circumstances, rituximab†) should be commenced with MTX. (LoE 1b, GoR A, SoR 9.2±1.2, 90%) • If a first bDMARD has failed, patients should be treated with another bDMARD; if a first TNF inhibitor therapy has failed, patients may receive another TNF inhibitor* or a biological agent with another mode of action. (LoE 1a, GoR A, SoR 9.4±0.8, 97%) * TNF inhibitors: adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, biosimilars (as approved according to a thorough approval process, such as by EMA and/or FDA). † - The 'certain circumstances', which include history of lymphoma or a demyelinating disease, are detailed in the accompanying text: – Rituximab approved for use after patients have responded insufficiently to TNF blockers – trial data in patients who were naive for csDMARDs and those who had an inadequate response to csDMARDs published (level 1 evidence) – in presence of certain contraindications for other agents – such as recent history of lymphoma, latent tuberculosis (TB) with contraindications to the use of chemoprophylaxis, living in a TB-endemic region, or a previous history of demyelinating disease – rituximab may be considered as a first-line biological agent – some rheumatologists also prioritise this drug in patients with a recent history of any malignancy, because rituximab use is not associated with the occurrence of cancers – rituximab is the least expensive biological agent at present
Bykerk VP et al., 2012 [3]. Recommendations for Pharmacological Management of Rheumatoid Arthritis with Traditional and Biologic Disease-	Canadian Rheumatology Association (CRA) **Fragestellungen** <u>Treatment with traditional DMARD</u> • When should combination therapy with traditional DMARD be used? • Which traditional DMARD combinations are preferred? • Should leflunomide be used in combination with MTX? <u>Treatment with biologic DMARD</u> • In patients being considered for treatment with biologic DMARD, how should an inadequate response to traditional DMARD be defined? • Which investigations should be ordered prior to starting treatment with biologic DMARD? • Should MTX be coprescribed with biologic DMARD?

modifying Antirheumatic Drugs	• When should anti-TNF therapy be used in the treatment of patients with RA? • When should abatacept be used in the treatment of patients with RA? • When should rituximab be used in the treatment of patients with RA? • How should patients be retreated with rituximab? • When should tocilizumab be used in the treatment of patients with RA? • Which therapeutic strategy is recommended after failure of 1 anti-TNF? • Which therapeutic strategy is recommended after failure of 2 anti-TNFs? • Which therapeutic strategy is recommended after failure of abatacept, rituximab, or tocilizumab? • Should therapy be tapered or withdrawn in RA patients who achieve sustained remission?
	Methodik evidenz- und konsensbasierte Leitlinie ***Grundlage der Leitlinie****:* synthesis of international guidelines (according to ADAPTE), supporting evidence, and expert consensus of a national Canadian RA working group including clinical (rheumatology and primary care), methodo-logical (epidemiologists/health services researchers/information specialist), rheumatology research trainees, and patient consumers ***Suchzeitraum****:* 01/2000 – 06/2010 ***Weitere Kriterien für die Qualität einer Leitlinie****:* • Leitlinie mit AGREE überprüft (Ergebnisse: “Recommend” (R), ”Recommend with Provisos” (R*), or “Would Not Recommend” (WNR)) • Aktualisierungsrecherchen durchgeführt • Quellen im jeweiligen Hintergrundtext zu den Empfehlungen zitiert ***LoE/GoR****:* we translated each guideline’s grading system onto a custom system for assigning levels of evidence simplified from that developed by the Scottish Intercollegiate Guideline Network (SIGN) (siehe Anlage 3 zu dieser Synopse) ***Sonstige methodische Hinweise:*** • Funded through the Canadian Institutes of Health Research (CIHR) and matched funds from the Canadian Rheumatology Association (CRA). • Potential conflicts for each working group member including industry funding, consultancies, commercial interests, and direct involvement in any guidelines included in the systematic review for the last 3 years are shown in Appendix 1.
	Empfehlungen <u>Treatment with MTX/DMARD</u> • Initial combination therapy with traditional DMARD should be considered, particularly in patients with poor prognostic features, moderate-high disease activity, and in patients with recent-onset disease. Combination therapy should also be considered in patients who have an inadequate response to monotherapy (Level I; Strength B) 5 CPG and 3 CS (AGREE rating: R=4, R*=3, WNR=1) • When treating with combination therapy, MTX should be used as the anchor drug unless contraindicated. Combinations not including MTX can be considered on a case-by-case basis. (Level I; Strength A) 4 CPG and 2 CS (AGREE rating: R=2, R*=3, WNR=1) • Combination therapy with leflunomide and MTX should be used with caution as it

	is associated with higher toxicity, (gastrointestinal and liver) (I) and has no added benefit relative to other DMARD combinations (IV) (Level I, IV; Strength A) 1 CPG and 5 CS (AGREE rating: R=1, R*=5) <u>Treatment with biologics</u> • In patients being considered for biologic therapy, an inadequate response to DMARD (DMARD-IR) is defined as moderate to high disease activity despite treatment with at least 2 DMARD [including MTX unless contraindicated] in mono or combination therapy after 3 months at target dose. (Level IV; Strength D) 10 CPG and 7 CS (AGREE rating: R=3, R*=14) • MTX co-prescription with biologics is recommended for improved efficacy. (Level I; Strength A) 9 CPG and 4 CS (AGREE rating: R=4, R*=9) • Anti-TNF therapy is recommended for the treatment of patients with RA after an inadequate response to DMARD. In exceptional circumstances involving patients with DMARD contraindications or high disease activity and poor prognostic factors (particularly early dis-ease), anti-TNF therapy may be an option after failure of DMARD monotherapy or in DMARD-naive patients. (Level I; Strength A) 8 CPG and 10 CS (AGREE rating: R=5, R*=12, WNR=1) • Abatacept is recommended for the treatment of patients with RA after an inadequate response to DMARD or anti-TNF therapy. (Level I; Strength A) 6 CPG and 1 CS (AGREE ratings: R=4, R*=3) • Rituximab is recommended for the treatment of patients with RF-positive RA after an inadequate response to DMARD or anti-TNF therapy. (Level I; Strength A) 7 CPG and 3 CS (AGREE rating: R=5, R*=5) • In patients who have failed treatment with 1 anti-TNF agent due to lack of efficacy or toxicity the following options are recommended: switch to another anti-TNF agent (I, II); switch to another biologic with a different mechanism of action [abatacept (ABAT), rituximab (RTX), tocilizumab (TCZ)] (I); or add MTX (or other DMARD) if the anti-TNF agent was used in monotherapy (II). (Level I, II; Strength B) 5 CPG (AGREE rating: R=2, R*=3) • In patients who have failed treatment with 2 anti-TNF agents a switch to another biologic with a different mechanism of action [abatacept (ABAT), rituximab (RTX), tocilizumab (TCZ)] is recommended. (Level II/IV; Strength C), no guideline • In the absence of data on therapeutic strategies after failure of abatacept (ABAT), rituximab (RTX), or tocilizumab (TCZ), the following options can be considered: switch to any biologic not previously tried and failed, add/switch to a traditional DMARD not previously tried and failed, or enroll the patient in a clinical trial with a new agent. (Level IV; Strength D), no guideline
Singh JA et al., 2012 [41]. 2012 Update of the 2008 Recom-mendations for the Use of Disease-Modifying Antirheumatic Drugs and Biologic Agents in the Treatment of	American College of Rheumatology (ACR) **Fragestellungen** 1) indications for DMARDs and biologic agents 2) switching between DMARD and biologic therapies
	Methodik evidenz- und konsensbasierte Leitlinie ***Grundlage der Leitlinie:*** systematic literature review, development of clinical scenarios, rating the appropriateness of clinical scenarios, conversion of clinical scenarios to ACR RA treatment recommendations, peer review ***Suchzeitraum:*** February 26, 2010 for the efficacy and safety studies ***LoE und GoR:***

Rheumatoid Arthritis	• Level of Evidence A: Data derived from multiple RCTs. • Level of Evidence B: Data derived from a single randomized trial, or nonrandomized studies. • Level of Evidence C: Only consensus opinion of experts, case studies, or standard-of-care. ***Sonstige methodische Hinweise:*** • Supported by a research grant from the ACR CoI declared
	Empfehlungen <u>Established RA:</u> <u>Initiating and switching among DMARDs</u> (…) 2) If after 3 months of methotrexate or methotrexate/DMARD combination, a patient still has moderate or high disease activity, then add another non-methotrexate DMARD or switch to a different non-methotrexate DMARD. <u>Switching from DMARDs to biologic agents</u> 3) If a patient has moderate or high disease activity after 3 months of methotrexate monotherapy or DMARD combination therapy, as an alternative to the DMARD recommendation just noted above, the panel recommends adding or switching to an anti-TNF biologic, abatacept, or rituximab (level of evidence A-C). If after 3 months of intensified DMARD combination therapy or after a second DMARD, a patient still has moderate or high disease activity, add or switch to an anti-TNF biologic (level of evidence C). <u>Switching among biologic agents due to lack of benefit or loss of benefit.</u> 4) If a patient still has moderate or high disease activity after 3 months of anti-TNF biologic therapy and this is due to a lack or loss of benefit, switching to another anti-TNF biologic or a non-TNF biologic is recommended. If a patient still has moderate or high disease activity after 6 months of a non-TNF biologic and the failure is due to a lack or loss of benefit, switch to another non-TNF biologic or an anti-TNF biologic (level of evidence B and C). <u>Switching among biologic agents due to harms/adverse events.</u> If a patient has moderate or high disease activity after failing an anti-TNF biologic because of a non-serious AE, switch to another anti-TNF biologic or a non-TNF biologic (level of evidence B and C). If a patient has moderate or high disease activity after failing a non-TNF biologic because of an AE (serious or non-serious), switch to another non-TNF biologic or an anti-TNF biologic (level of evidence C).
National Institute for Health and Care Excellence, 2009 [32]. **last updated 2015**	**Zielsetzung/Fragestellung:** Clinical guideline
	Methodik Methodenreport beschreibt systematische Evidenzaufbereitung und Konsensusprozesse (je nach Bedarf fomal oder informal) - eigene Checklisten - Anwendung von GRADE - GoR schlagen sich in den Formulierungen wider ""To avoid giving the impression that higher grade recommendations are of higher priority for implementation, NICE no longer assigns grades to recommendations." <u>Update information:</u> Recommendations have been added on hand exercise programmes for people (adults) with rheumatoid arthritis. These are marked as [new 2015]. Where recommendations end [2009], the evidence has not been reviewed since the original guideline.

Rheumatoid arthritis in adults: management	*Hinweis*: *'In 2015 we reviewed the evidence on hand exercise programmes and added 2 new recommendations'.* → diese betrafen jedoch nicht die pharmakologische Therapie **DMARDS** **Introducing and withdrawing DMARDs** • In people with newly diagnosed active RA, offer a combination of DMARDs (including methotrexate and at least one other DMARD, plus short-term glucocorticoids) as first-line treatment as soon as possible, ideally within 3months of the onset of persistent symptoms. [2009] • Consider offering short-term treatment with glucocorticoids (oral, intramuscular or intra-articular) to rapidly improve symptoms in people with newly diagnosed RA if they are not already receiving glucocorticoids as part of DMARD combination therapy. [2009] • In people with recent-onset RA receiving combination DMARD therapy and in whom sustained and satisfactory levels of disease control have been achieved, cautiously try to reduce drug doses to levels that still maintain disease control. [2009] • In people with newly diagnosed RA for whom combination DMARD therapy is not appropriate[2], start DMARD monotherapy, placing greater emphasis on fast escalation to a clinically effective dose rather than on the choice of DMARD. [2009] • In people with established RA whose disease is stable, cautiously reduce dosages of disease-modifying or biological drugs. Return promptly to disease controlling dosages at the first sign of a flare. [2009] • When introducing new drugs to improve disease control into the treatment regimen of a person with established RA, consider decreasing or stopping their pre-existing rheumatological drugs once the disease is controlled. [2009] • In any person with established rheumatoid arthritis in whom disease-modifying or biological drug doses are being decreased or stopped, arrangements should be in place for prompt review. [2009] **Glucocorticoids** • Offer short-term treatment with glucocorticoids for managing flares in people with recent-onset or established disease to rapidly decrease inflammation. [2009] • In people with established RA, only continue long-term treatment with glucocorticoids when: ○ the long-term complications of glucocorticoid therapy have been fully discussed, and ○ all other treatment options (including biological drugs) have been offered. [2009] **Biological drugs** • On the balance of its clinical benefits and cost effectiveness, anakinra is not recommended for the treatment of RA, except in the context of a controlled, long-term clinical study. [2009] • Patients currently receiving anakinra for RA may suffer loss of wellbeing if their treatment were discontinued at a time they did not anticipate. Therefore, patients should continue therapy with anakinra until they and their consultant consider it is appropriate to stop. [2009] • Do not offer the combination of tumour necrosis factor-α (TNF-α) inhibitor therapy and anakinra for RA. [2009]

Deutsche Gesellschaft für Rheumatologie, 2011 [9]. Management der frühen rheumatoiden Arthritis (S3)	AWMF Leitlinie (S3)
	Methodik ***Grundlage der Leitlinie***: – interdisziplinären Leitliniengruppe – Systematische Recherche, Auswahl und Bewertung der Literatur, Erstellung von Evidenztabellen – Formale Konsensfindung (nominaler Gruppenprozess ***Suchzeitraum***: bis 2009 ***LoE und GoR:*** ↑↑ Diesen Empfehlungen liegen Studien mit großer Ergebnissicherheit zugrunde, die einen eindeutigen Nutzen gegenüber Risiko belegen. ↑ Diesen Empfehlungen liegen Studien zugrunde mit eingeschränkter Ergebnissicherheit und/oder geringerem Nutzen gegenüber Risiko. Good Clinical Practice ist eine Empfehlung der Konsensgruppe
	Empfehlungen • Sorgen Sie dafür, dass Ihre Patienten von der Diagnosestellung an mit klassischen DMARDs behandelt werden, um eine Verzögerung der Krankheitsprogression zu erzielen und damit die Langzeitprognose zu verbessern. **(LoE: ↑↑)** **<u>Wahl der Basistherapie</u>** • Setzen Sie Methotrexat als Mittel der ersten Wahl als Monotherapie und als Kombinationspartner bei der Behandlung mit klassischen DMARD ein. (LoE: ↑↑) <u>Erläuterung zur Wahl der Basistherapie:</u> Die allgemeinen Daten zur Therapie mit klassischen DMARDs belegen die Vorteile einer Methotrexat-Therapie aufgrund des relativ schnellen Ansprechens und der längerfristigen Kontrolle der Erkrankung (basierend auf 7 älteren Literaturangaben). Kann Methotrexat nicht verwendet werden (z.B. bei Unverträglichkeit oder Kontraindikationen), kann ein guter Therapieerfolg auch mit anderen klassischen DMARDs erreicht werden. <u>Weitere Erläuterungen aus Fazit bei 5.1.6 DMARD-Kombinationstherapie:</u> In der Regel ist Methotrexat (meist in Kombination mit einem Glucocorticoid) als Ersttherapie der ERA empfohlen, in etwa 20–30 % kann damit bereits eine Remission erreicht werden. Bei nicht ausreichendem Ansprechen ist die Zugabe eines weiteren DMARD normalerweise der nächste Schritt. Biologika sind bei früher RA monotherapeutisch dem Methotrexat nicht überlegen, in Kombination mit Methotrexat jedoch deutlich besser wirksam als klassische DMARDs und deshalb bei DMARD-Versagen die nächste Option. • Unterdrücken Sie bis zum Erreichen der Wirkung der Basistherapie die Krankheitsaktivität mit einer Glucocorticoid-Therapie. **(LoE: ↑↑)** • Führen Sie zusätzlich zur Therapie mit klassischen DMARDs die Glucocorticoid-Therapie niedrig dosiert fort, um die radiologisch nachweisbare Gelenkzerstörung zu verzögern. **(LoE: ↑↑)**
Scottish Intercollegiate Guidelines Network, 2011	**Fragestellung** This guideline addresses the diagnosis of early RA, its pharmacological treatment including symptom relief and disease modification, and the role of the multidisciplinary team in improving the care of patients with RA.

[39]. Management of early rheumatoid arthritis

Methodik

SIGN guidelines are developed by multidisciplinary groups of practising clinicians using a standard methodology based on a systematic review of the evidence. Further details about SIGN and the guideline development methodology are contained in SIGN 50: A Guideline Developer's handbook

Suchzeitraum: 2003-2009

LoE and GoR

LoE	
1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1 -	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort studies, high quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2 -	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

GoR	
A	At least one meta-analysis, systematic review, or RCT rated as 1++,and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+
GOOD PRACTICE POINTS	Recommended best practice based on the clinical experience of the guideline development group

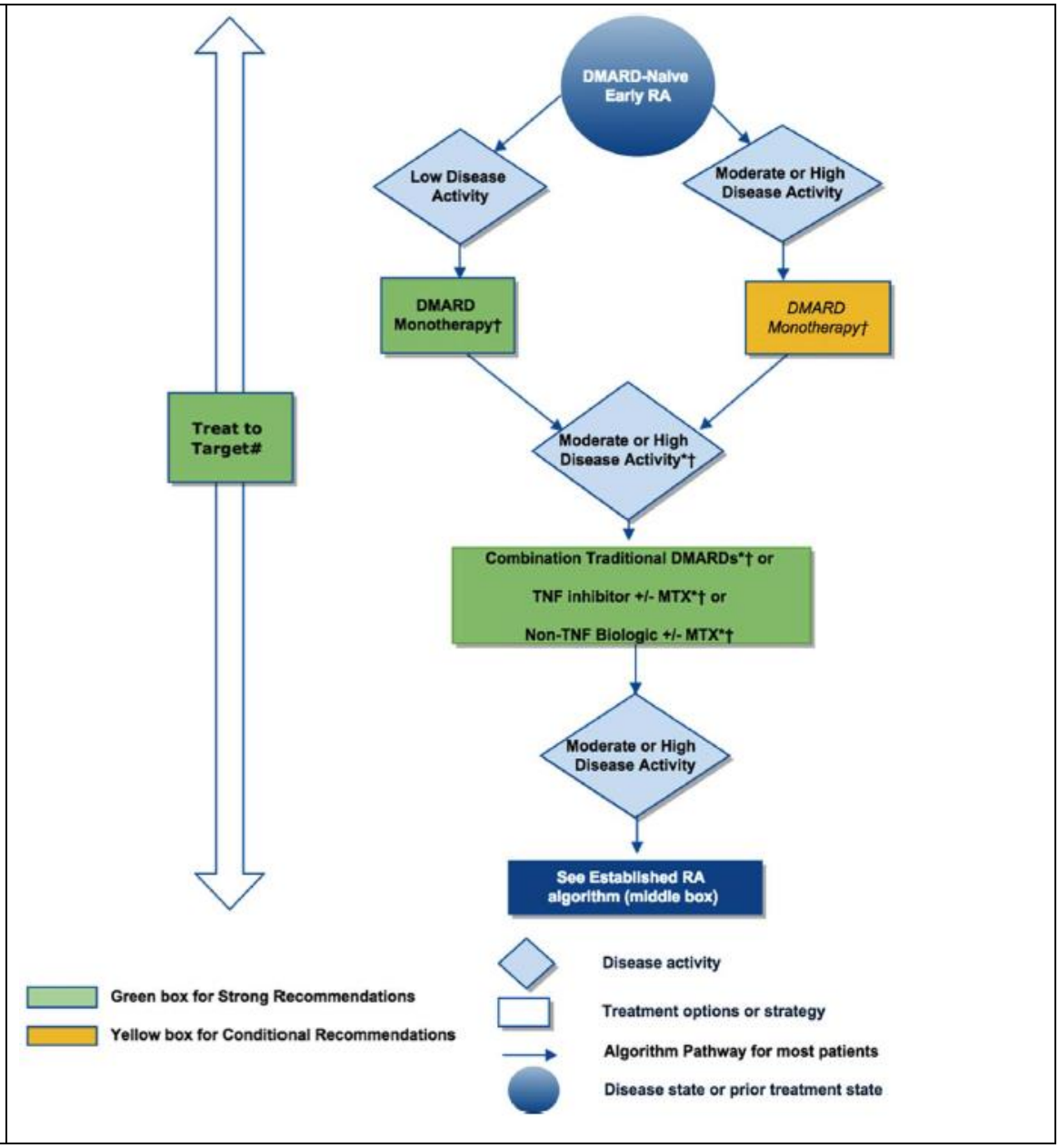
	• Early initiation of treatment with DMARDs is recommended to control the symptoms and signs of RA as well as limiting radiological damage. **(LoE: B)** **<u>DISEASE MODIFYING ANTI-RHEUMATIC DRUGS</u>** • Methotrexate and sulfasalazine are the DMARDs of choice due to their more favorable efficacy and toxicity profiles. **(GoR: A)** A systematic review found leflunomide (LEF), methotrexate (MTX) and sulfasalazine (SASP) to have comparable efficacy. MTX has the most favourable efficacy/toxicity trade-off. **(LoE: 1++)** • A combination DMARD strategy, rather than sequential monotherapy, should be considered in patients with an inadequate response to initial DMARD therapy **(GoR A)** A systematic review of three RCTs concluded that combination therapy is more effective than sequential monotherapy in improving the symptoms and signs, physical function, and reducing radiographic progression. Most combinations use MTX as an anchor drug. **(LoE 1++)** **Biologics** • A meta-analysis of seven RCTs involving 2,673 patients compared combination therapy with MTX and biologic (1,248 patients) to MTX alone (1,152). The biologics studied were infliximab, adalimumab, etanercept, and abatacept. The authors concluded that remission rates at one year were greater in the combination therapy groups, than MTX monotherapy. In the combination group significantly more achieved clinical remission but there was only a modest benefit on radiological non-progression. All of the biologic agents had a similar efficacy for clinical remission.(LoE 1++) • In an RCT of a TNF-α inhibitor in patients with early moderate to severe RA (DAS28 ≥3.2), the addition of infliximab to those with an inadequate response (DAS28 ≥3.2) to MTX was found to achieve a good EULAR response in more patients than the addition of HCQ and SASP to MTX.73 This has yet to be shown to be cost effective (LoE 1++) • Use of TNF-α inhibitors for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with MTX or other DMARDs is not recommended (LoE 1++)
Singh JA et al., 2016 [43]. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis	Fragestellung/Zielsetzung: This guideline addresses 6 major topics: 1) use of traditional disease-modifying antirheumatic drugs (traditional/conventional DMARDs, herein referred to as DMARDs), biologic DMARDs (herein referred to as biologics), and tofacitinib, including tapering and discontinuing medications, and a treat-to-target approach; 2) use of glucocorticoids; 3) use of biologics and DMARDs in high-risk populations (i.e., those with hepatitis, congestive heart failure, malignancy, and serious infections); 4) use of vaccines in patients starting/receiving DMARDs or biologics; 5) screening for tuberculosis (TB) in the context of biologics or tofacitinib; and 6) laboratorymonitoring for traditional DMARDs.
	Methodik Grundlage der Leitlinie We developed this guideline following the recently revised ACR guideline development process (http://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-

Practice-Guidelines). This process includes the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology (available at www.gradeworkinggroup.org)

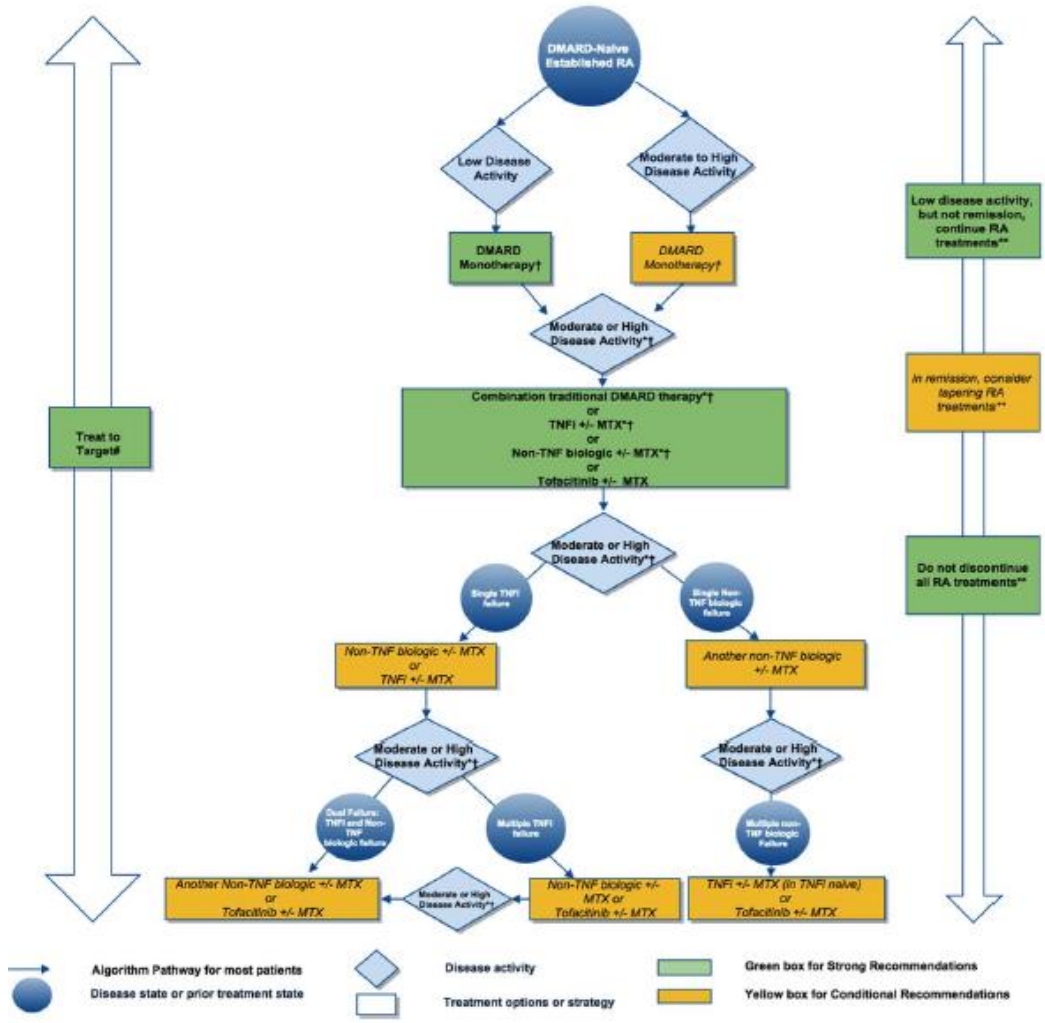
Sonstige methodische Hinweise: Systematische Literarturrecherche

Empfehlungen:

Recommendations for patients with symptomatic Early RA	Level of Evidence (evidence reviewed)
1. Regardless of disease activity level, use a treat-to-target strategy rather than a non-targeted approach (PICO A.1).	**Low (17)**
2. If the disease activity is low, in patients who have never taken a DMARD: **• use DMARD monotherapy (MTX preferred) over double therapy (PICO A.2).** **• use DMARD monotherapy (MTX preferred) over triple therapy (PICO A.3).**	**Low (18-21)** **Low (22-25)**
3. If the disease activity is moderate or high, in patients who have never taken a DMARD: *• use DMARD monotherapy over double therapy (PICO A.4).* *• use DMARD monotherapy over triple therapy (PICO A.5).*	*Moderate (18,20,21)* *High (22-25)*
4. If disease activity remains moderate or high despite DMARD monotherapy (with or without glucocorticoids), use combination DMARDs or a TNFi or a non-TNF biologic (all choices with or without MTX, in no particular order of preference), rather than continuing DMARD monotherapy alone (PICO A.7).	**Low (26-28)**
5. If disease activity remains moderate or high despite DMARDs: *• use a TNFi monotherapy over tofacitinib monotherapy (PICO A.8).* *• use a TNFi + MTX over tofacitinib + MTX (PICO A.9).*	*Low (29)* *Low (30)*
6. If disease activity remains moderate or high despite DMARD (PICO A.6) or biologic therapies (PICO A.12), add low-dose glucocorticoids.	*Moderate (31-37)* *Low (31-37)*
7. If disease flares, add short-term glucocorticoids at the lowest possible dose and for the shortest possible duration (PICO A.10, A.11).	*Very low (38-43)*


DMARD-Naive Early RA
Low Disease Activity
Moderate or High Disease Activity
DMARD Monotherapy†
DMARD Monotherapy†
Treat to Target#
Moderate or High Disease Activity*†
Combination Traditional DMARDs*† or
TNF inhibitor +/- MTX*† or
Non-TNF Biologic +/- MTX*†
Moderate or High Disease Activity
See Established RA algorithm (middle box)
Green box for Strong Recommendations
Yellow box for Conditional Recommendations
Disease activity
Treatment options or strategy
Algorithm Pathway for most patients
Disease state or prior treatment state

Recommendations for patients with Established RA[1]	Level of Evidence (evidence reviewed)
1. Regardless of disease activity level, use a treat-to-target strategy rather than a non-targeted approach (PICO B.1).	**Moderate (44-46)**
2. If the disease activity is low, in patients who have never taken a DMARD, use DMARD monotherapy (MTX preferred) over a TNFi (PICO B.2).	**Low (47,48)**
3. If the disease activity is moderate or high in patients who have never taken a DMARD: • *use DMARD monotherapy (MTX preferred) over tofacitinib (PICO B.3).* • *use DMARD monotherapy (MTX preferred) over combination DMARD therapy (PICO B.4).*	*High (49)* *Moderate (18,20-25)*
4. If disease activity remains moderate or high despite DMARD monotherapy, use combination traditional DMARDs or add a TNFi or a non-TNF biologic or tofacitinib (all choices with or without MTX, in no particular order of preference), rather than continuing DMARD monotherapy alone (PICO B.5).	**Moderate to Very low (23,26,29,30,47,48,50-59)**
5. If disease activity remains moderate or high despite TNFi therapy in patients who are currently not on DMARDs, add one or two DMARDs to TNFi therapy rather than continuing TNFi therapy alone (PICO B.6).	**High (60-65)**
6. If disease activity remains moderate or high despite use of a single TNFi: • *use a non-TNF biologic, with or without MTX, over another TNFi with or without MTX (PICO B.12 and B.14).* • *use a non-TNF biologic, with or without MTX, over tofacitinib with or without MTX (PICO B.13 and B.15).*	*Low to Very low (66-72)* *Very low[4]*
7. If disease activity remains moderate or high despite use of a single non-TNF biologic, use another non-TNF biologic, with or without MTX, over tofacitinib, with or without MTX (PICO B.16 and B.17).	*Very low[4]*
8. If disease activity remains moderate or high despite use of multiple (2+) sequential TNFi therapies, first use a non-TNF biologic, with or without MTX, over another TNFi or tofacitinib (with or without MTX) (PICO B.8, B.9, B.10, B.11).	*Very low (73-75)*
9. If the disease activity still remains moderate or high despite the use of multiple TNFi therapies, use tofacitinib, with or without MTX, over another TNFi, with or without MTX, if use of a non-TNF biologic is not an option (PICO B.23 and B.24).	*Low (29,30)*
10. If disease activity remains moderate or high despite use of at least one TNFi and at least one non-TNF-biologic: • *first use another non-TNF biologic, with or without MTX, over tofacitinib (PICO B.21 and B.22).* • *If disease activity remains moderate or high, use tofacitinib, with or without MTX, over another TNFi (PICO B.19 and B.20).*	*Very low (29,30)* *Very low (29)*
11. If disease activity remains moderate or high despite use of DMARD, TNFi, or non-TNF biologic therapy, add short-term, low dose glucocorticoid therapy (PICO B.26 and B.27).	*High to Moderate (33,41,76,77)*
12. If disease flares in patients on DMARD, TNFi, or non-TNF biologic therapy, add short-term glucocorticoids at the lowest possible dose and the shortest possible duration (PICO B.28 and B.29).	*Very low (40-43)*
13. If the patient is in remission: • *taper DMARD therapy (PICO B.31)[2].* • *taper TNFi, non-TNF biologic, or tofacitinib (PICO B.33, B.35, B.37) (please also see #15).*	*Low[3] (78)* *Moderate to Very low[3] (79,80)*
14. If disease activity is low: • **continue DMARD therapy (PICO B.30).** • **continue TNFi, non-TNF biologic or tofacitinib rather than discontinuing respective medication (PICO B.32, B.34 and B.36).**	**Moderate (78)** **High to Very low (79,80)**
15. If the patient's disease is in remission, do not discontinue all RA therapies (PICO B.38).	**Very low[4]**

	
Smolen JS et al., 2016 [44]. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force	Fragestellung/Zielsetzung: To update the 2010 treat-to-target recommendations based on systematic literature reviews (SLR) and expert opinion. Methodik Grundlage der Leitlinie A task force of rheumatologists, patients and a nurse specialist assessed the SLR results and evaluated the individual items of the 2010 recommendations accordingly, reformulating many of the items. These were subsequently discussed, amended and voted upon by >40 experts, including 5 patients, from various regions of the world. Levels of evidence, strengths of recommendations and levels of agreement were derived. Sonstige methodische Hinweise: Update von 2010

Recommendation

Table 1 The updated recommendations (2014), including a comparison with the 2010 version

Overarching principles*

2014	2010†
A. The treatment of rheumatoid arthritis must be based on a shared decision between patient and rheumatologist	A. The treatment of rheumatoid arthritis must be based on a shared decision between patient and rheumatologist
B. The primary goal of treating patients with rheumatoid arthritis is to maximise long-term health-related quality of life through control of symptoms, prevention of structural damage, normalisation of function and participation in social and work-related activities	B. The primary goal of treating the patient with rheumatoid arthritis is to maximise long-term health-related quality of life through control of symptoms, prevention of structural damage, normalisation of function and social participation
C. Abrogation of inflammation is the most important way to achieve these goals	C. Abrogation of inflammation is the most important way to achieve these goals
D. Treatment to target by measuring disease activity and adjusting therapy accordingly optimises outcomes in rheumatoid arthritis	D. Treatment to target by measuring disease activity and adjusting therapy accordingly optimises outcomes in rheumatoid arthritis

Final set of 10 recommendations on treating rheumatoid arthritis to target based on both evidence and expert opinion*

2014	2010
1. The primary target for treatment of rheumatoid arthritis should be a state of clinical remission	1. The primary target for treatment of rheumatoid arthritis should be a state of clinical remission
2. Clinical remission is defined as the absence of signs and symptoms of significant inflammatory disease activity	2. Clinical remission is defined as the absence of signs and symptoms of significant inflammatory disease activity
3. While remission should be a clear target, low-disease activity may be an acceptable alternative therapeutic goal, particularly in long-standing disease	3. While remission should be a clear target, based on available evidence low-disease activity may be an acceptable alternative therapeutic goal, particularly in established long-standing disease
4 The use of validated composite measures of disease activity, which include joint assessments, is needed in routine clinical practice to guide treatment decisions	6. The use of validated composite measures of disease activity, which include joint assessments, is needed in routine clinical practice to guide treatment decisions
5 The choice of the (composite) measure of disease activity and the target value should be influenced by comorbidities, patient factors and drug-related risks	9. The choice of the (composite) measure of disease activity and the level of the target value may be influenced by consideration of comorbidities, patient factors and drug-related risks
6. Measures of disease activity must be obtained and documented regularly, as frequently as monthly for patients with high/moderate disease activity or less frequently (such as every six months) for patients in sustained low-disease activity or remission	5. Measures of disease activity must be obtained and documented regularly, as frequently as monthly for patients with high/moderate disease activity or less frequently (such as every 3–6 months) for patients in sustained low-disease activity or remission
7. Structural changes, functional impairment and comorbidity should be considered when making clinical decisions, in addition to assessing composite measures of disease activity	7. Structural changes and functional impairment should be considered when making clinical decisions, in addition to assessing composite measures of disease activity
8. Until the desired treatment target is reached, drug therapy should be adjusted at least every three months *	4. Until the desired treatment target is reached, drug therapy should be adjusted at least every three months
9. The desired treatment target should be maintained throughout the remaining course of the disease	8. The desired treatment target should be maintained throughout the remaining course of the disease
10. The rheumatologist should involve the patient in setting the treatment target and the strategy to reach this target	10. The patient has to be appropriately informed about the treatment target and the strategy planned to reach this target under the supervision of the rheumatologist

The actual changes are highlighted in the online supplementary table.
*As worded, these recommendations constitute solely a brief summary of the discussions on individual aspects of the Task Force's activity. The Task Force specifies that these recommendations must not be interpreted without taking the respective text accompanying each item into account.
†The numbers at the left of the 2010 recommendations refer to the original numbering at that time.

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

National Institute for Health and Care Excellence (NICE), 2010 [30]. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor. NICE technology appraisal guidance 195	1) Rituximab in combination with MTX is recommended as an option for the treatment of adults with severe active RA who have had an inadequate response to, or are intolerant of, other DMARDs, including at least one TNF inhibitor. Treatment with rituximab should be given no more frequently than every 6 months. 2) Treatment with rituximab in combination with MTX should be continued only if there is an adequate response following initiation of therapy and if an adequate response is maintained following retreat-ment with a dosing interval of at least 6 months. An adequate response is defined as an improvement in DAS28 of 1.2 points or more. 3) Adalimumab, etanercept, infliximab and abatacept, each in combination with MTX, are recommended as treatment options only for adults with severe active RA who have had an inadequate response to, or have an intolerance of, other DMARDs, including at least one TNF inhibitor, and who cannot receive rituximab therapy because they have a contraindication to rituximab, or when rituximab is withdrawn because of an AE. 4) Adalimumab monotherapy and etanercept monotherapy are recommended as treatment options for adults with severe active RA who have had an inadequate response to, or have an intolerance of, other DMARDs, including at least one TNF inhibitor, and who cannot receive rituximab therapy because they have a contraindication to MTX, or when MTX is withdrawn because of an AE. 5) Treatment with adalimumab, etanercept, infliximab and abatacept should be continued only if there is an adequate response (as defined in 1.2) 6 months after initiation of therapy. Treatment should be monitored, with assessment of DAS28, at least every 6 months and continued only if an adequate response is maintained. 6) When using DAS28, healthcare professionals should take into account any physical, sensory or learning disabilities, communication difficulties, or disease characteristics that could adversely affect patient assessment and make any adjustments they consider appropriate. 7) A team experienced in the diagnosis and treatment of RA and working under the supervision of a rheumatologist should initiate, supervise and assess response to treatment with rituximab, adalimumab, etanercept, infliximab or abatacept.
National Institute for Health and Care Excellence (NICE), 2011 [31]. Golimumab for the treatment of rheumatoid arthritis after the failure of	1) Golimumab in combination with methotrexate is recommended as an option for the treatment of RA in adults whose RA has responded in-adequately to conventional DMARDs only, including methotrexate, if: • it is used as described for other TNF inhibitor treatments in 'Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis' (NICE technology appraisal guidance 130), **and** • the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose, agreed as part of the patient access scheme. 2) Golimumab in combination with methotrexate is recommended as an option for the treatment of RA in adults whose RA has responded inadequately to other DMARDs, including a TNF

previous disease-modifying anti-rheumatic drugs. NICE technology appraisal guidance 225	inhibitor, if: • it is used as described for other TNF inhibitor treatments in 'Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor' (NICE technology appraisal guidance 195), **and** • the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose, agreed as part of the patient access scheme. 3) When using the DAS28, healthcare professionals should take into account any physical, sensory or learning disabilities, communication difficulties, or disease characteristics that could adversely affect patient assessment and make any adjustments they consider appropriate.
National Institute for Health and Care Excellence (NICE), 2012 [33]. Tocilizumab for the treatment of rheumatoid arthritis. NICE technology appraisal guidance 247	1) Tocilizumab in combination with methotrexate is recommended as an option for the treatment of RA in adults, if: • the disease has responded inadequately to DMARDs **and** it is used as described for TNF inhibitor treatments in 'Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis' (NICE technology appraisal guidance 130), specifically the recommendations on disease activity and choice of treatment **or** • the disease has responded inadequately to DMARDs and a TNF inhibitor and the person cannot receive rituximab because of a contraindication to rituximab, or because rituximab is withdrawn because of an AE, and tocilizumab is used as described for TNF inhibitor treatments in'Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of RA after the failure of a TNF inhibitor' (NICE technology appraisal guidance 195), specifically the recommendations on disease activity **or** • the disease has responded inadequately to one or more TNF inhibitor treatments and to rituximab **and** • the manufacturer provides tocilizumab with the discount agreed as part of the patient access scheme. 2) People currently receiving tocilizumab for the treatment of RA who do not meet the criteria in 1) should have the option to continue treat-ment until they and their clinicians consider it appropriate to stop.

Anlage 1

Patientenrelevante Endpunkte aus IQWiG 2013

Tabelle 15: Operationalisierung der Zielgrößen in den Einzelstudien

Patientenrelevante Endpunkte der Nutzenbewertung	**Operationalisierung der Zielgrößen in den Studien[a]**
Remission	▪ ACR 100 ▪ ACR Remission ▪ DAS 28 (CRP)[b] < 2,6, DAS 28 (BSG)[c] < 2,6 ▪ Pinals-Kriterien
Symptomatik der rheumatoiden Arthritis (insbesondere Schmerz, Fatigue, Morgensteifigkeit)	▪ schmerzhafte / empfindliche Gelenke[d] ▪ geschwollene Gelenke ▪ Schmerz (VAS) ▪ globale Erhebung der Krankheitsaktivität durch den Patienten ▪ allgemeiner Gesundheitszustand des Patienten (VAS) ▪ Morgensteifigkeit ▪ Fatigue (FACIT-F, VAS, FAS) ▪ Schlafqualität (MOS-Schlaf-Fragebogen)
Strukturelle Gelenkveränderungen (wie Deformitäten, Versteifungen, Kontrakturen)	Es konnten keine Zielgrößen der eingeschlossenen Studien diesem patientenrelevanten Endpunkt zugeordnet werden.
Körperlicher Funktionsstatus einschließlich Aktivitäten des täglichen Lebens	▪ HAQ ▪ HAQ-DI ▪ mHAQ ▪ MDHAQ
Soziales Funktionsniveau (Teilhabe am beruflichen und sozialen Leben)	▪ WPAI ▪ Fragen zum Arbeitsausfall, zur Arbeitsfähigkeit und zur Leistungsfähigkeit

Patientenrelevante Endpunkte der Nutzenbewertung	**Operationalisierung der Zielgrößen in den Studien[a]**
Gesundheitsbezogene Lebensqualität	▪ SF-36 ▪ SF-12 ▪ EQ-5D ▪ HUI
Gesamtmortalität	Todesfälle
Unerwünschte Arzneimittelwirkungen	▪ Gesamtrate unerwünschter Ereignisse ▪ Gesamtrate schwerwiegender unerwünschter Ereignisse ▪ Gesamtrate Studienabbrüche wegen unerwünschter Ereignisse ▪ Gesamtrate Infektionen ▪ Gesamtrate schwerwiegender Infektionen

a: Beschreibung der Instrument siehe Anhang E
b: DAS 28 unter Verwendung des Entzündungsparameters CRP. Im vorliegenden Bericht wird in den Ergebnistabellen vermerkt, welcher Entzündungsparameter verwendet wurde.
c: DAS 28 unter Verwendung des Entzündungsparameters BSG. Im vorliegenden Bericht wird in den Ergebnistabellen vermerkt, welcher Entzündungsparameter verwendet wurde.
d: im weiteren Verlauf des vorliegenden Berichts als „schmerzhaft" benannt

ACR: American College of Rheumatology, DAS: Disease Activity Score, EQ-5D: EuroQol-5D, FACIT-F: Funtcional Assessment of Chronic Illness Therapy – Fatigue, FAS: Fatigue Assessment Scale, HAQ-DI: Health Assessment Questionnaire-Disability Index, HUI: Health Utility Index, mHAQ: modified Health Assessment Questionnaire, MDHAQ: multidimensionaler Health Assessment Questionnaire, MOS: Medical Outcomes Study, SF: Health Survey Short Form, VAS: visuelle Analogskala, WPAI: Work Productivity and Activity Impairment

Anlage 2

Michaud et al. 2015: Übersicht der Ergebnisse bisheriger MA zur Sicherheit von TNF-Inhibitoren

Table 3 Summary of Previous Meta-Analyses on Serious Adverse Events Associated with Use of Biologics in Rheumatoid Arthritis

Author, Year	Interventions	Included Studies, N	Total Subjects	Study Design	Minimum Duration	SAE (Overall)	Malignancy	Serious Infection	Discontinuation due to AEs
Bongartz, 2006[2]	ADA, INF	9	5,005	RCT	> 12 wks	NA	↑ (RR=3.3)	↑ (RR=2.0)	NA
Chen (NICE) , 2006[73]	ADA, ETN, INF	29	9,869	RCT	NA	↔	↔	↔ (overall) ↑ (INF)	↔ (overall) ↑ (INF)
Alonso-Ruiz, 2008[74]	ADA, ETN, INF	13	7,087	RCT	> 24 wks	↔	↔	↔ (overall) ↑ (INF)	↔ (overall) ↑ (ADA, INF) ↓ (ETN)
Bongartz, 2009[75]	ETN	9	3,316	RCT	> 12 wks	NA	↔	NA	NA
Leombruno, 2009[3]	ADA, ETN, INF	23 papers (18 RCTs)	8,808	RCT	> 10 wks	↔	↔	↔ (overall) ↑ (high dose 2x)	NA
Singh, 2009[76]	ADA, ETN, INF, ABT, ANK, RTX	31	NA	RCT	NA	NA	NA	NA	↔ (overall) ↑ (ADA, INF)
Wiens, 2009[77]	ETN	8	2,385	RCT	NA	↔	↔	↔	↔
Wiens, 2009[78]	INF	7	2,129	RCT	NA	↔	↔	↔	↑
Singh (CR), 2010[79]	GLM	4	1,714	RCT/ CCT	NA	↔	↔	↔	↔
Wiens, 2010[80]	ADA, ETN, INF	21	6,503	RCT	NA	↔	↔	↔	↔ (overall) ↑ (ADA, INF)
Askling, 2011[81]	ADA, ETN, INF	74	22,904	RCT	> 4 wks	NA	↔ (overall) ↑ (skin cancer)	NA	NA
Ruiz Garcia (CR), 2011[82]	CZP	5	2,094	RCT	NA	↑ (RR=2.02)	↔	↑ (RR>3)	↑ (RR=1.93)
Singh (CR), 2011*[5]	9 biologics†	160 RCTs, 46 OLEs	60,630	RCT, CCT, OLE	NA	↔	↔	↑ (OR = 1.55 in RA)	↔
Thompson, 2011[4]	ADA, CZP, ETN, GLM, INF	6 (early RA)	3,419	RCT	> 24 wks	NA	↔	↔	NA
Aaltonen, 2012[6]	ADA, CZP, ETN, GLM, INF	40 papers (26 RCTs)	9,862	RCT	NA	↔ (overall) ↑ (CZP)	NA	↔	↔ (overall) ↑ (ADA, CZP, INF) ↓ (ETN, RR = 0.71 compared with control)
Lopez-Olivo, 2012*[7]	9 biologics†	63	29,423	RCT	> 24 wks	NA	↔	NA	NA
Lethaby (CR), 2013[83]	ETN	9	2,842	RCT/CCTs	> 24 wks	↔	↔	↔	↓ (RR=0.53 for ETN + DMARDs vs. DMARD)
Current Study	**ADA, CZP, ETN, GLM, INF**	**44 papers (38 RCTs)**	**17,601**	**RCT**	**> 12 weeks**	**↔ ↑ (CZP)**	**↔**	**↑ (overall) ↑ (ADA, CZP, INF)**	**↑ (overall) ↑ (ADA, CZP, INF) ↓ (ETN, OR = 0.72)**

ADA = adalimumab; CZP = certolizumb pegol; ETN = etanercept; INF = infliximab; GLM = golimumab; ABT = abatacept; ANK = anakinra; RTX = rituximab; TCZ = tocilizumab; MTX = methotrexate; DMARD = disease-modifying antirheumatic drug; RR = relative risk; RD = risk difference; RCT = randomized controlled trial; CCT = controlled Clinical trial; OLE = open-label extension; SAE = serious adverse event; AEs = adverse events; NE = not estimable; NICE = National Institute for Clinical Excellence; CR = Cochrane Reviews.

*The results are based on all indications of the 9 biologics invested in that study, unless marked otherwise.

†ADA, CZP, ETN, GLM, INF, ABT, ANK, RTX and TCZ.

Anlage 3

Evidenzklassifizierung aus *Bykerk 2012*

Table 2. Custom system for assigning level of evidence and strength of recommendation.

Levels of Evidence		Strength of Recommendation	
I	Metaanalyses, systematic reviews of RCT, or individual RCT	A	Strong recommendation: • Direct level I evidence
II	Metaanalysis, systematic reviews of observational studies (cohort/case control studies), or individual observational studies OR RCT subgroup/post-hoc analyses	B	Moderate recommendation: • Direct level II evidence or extrapolated level I evidence
III	Nonanalytic studies, e.g., case reports, case series	C	Weak recommendation • Direct level III evidence or extrapolated level II evidence
IV	Expert opinion	D	Consensus recommendation: • Expert opinion based on very limited evidence
NR	Recommendations are not linked to evidence		

RCT: randomized controlled trial; NR: not reported.

Detaillierte Darstellung der Recherchestrategie:

Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database) **am 09.10.2015**

#	Suchfrage
1	MeSH descriptor: [Arthritis, Rheumatoid] explode all trees
2	(rheumatoid arthritis):ti (Word variations have been searched)
3	#1 or #2
4	#3 Publication Year from 2010 to 2015

SR, HTAs in Medline (PubMed) am 08.10.2015

#	Suchfrage
1	"arthritis, rheumatoid/therapy"[MeSH Terms]
2	rheumatoid arthritis[Title]
3	((((((((((treatment*[Title/Abstract]) OR therapy[Title/Abstract]) OR therapies[Title/Abstract]) OR therapeutic[Title/Abstract]) OR monotherap*[Title/Abstract]) OR polytherap*[Title/Abstract]) OR pharmacotherap*[Title/Abstract]) OR effect*[Title/Abstract]) OR efficacy[Title/Abstract]) OR treating[Title/Abstract]) OR treated[Title/Abstract]) OR management[Title/Abstract]) OR treat*[Title/Abstract]
4	(#2 AND #3)
5	(#1 OR #4)
6	(#5) AND (Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp])
7	(#5) AND (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))
8	(#6 OR #7)
9	(#8) AND ("2010/10/01"[PDAT] : "2015/10/08"[PDAT])

Leitlinien in Medline (PubMed) am 08.10.2015

#	Suchfrage
1	arthritis, rheumatoid[MeSH Terms]
2	rheumatoid arthritis[Title]
3	(#1 OR #2)
4	((((Guideline[Publication Type]) OR Practice Guideline[Publication Type]) OR Consensus Development Conference[Publication Type]) OR Consensus Development Conference, NIH[Publication Type]) OR guideline*[Title]
5	(#3 AND #4)
6	(#5) AND ("2010/10/01"[PDAT] : "2015/10/08"[PDAT])

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) **am 14.07.2016**

#	Suchfrage
1	MeSH descriptor: [Arthritis, Rheumatoid] explode all trees
2	(rheumatoid arthritis):ti (Word variations have been searched)

3	#1 or #2
4	#1 or #2 Publication Year from 2015 to 2016, in Cochrane Reviews (Reviews only) and Technology Assessments

SR, HTAs in Medline (PubMed) am 14.07.2016

#	Suchfrage
1	"arthritis, rheumatoid/therapy"[MeSH Terms]
2	rheumatoid arthritis[Title]
3	((((((((((treatment*[Title/Abstract]) OR therapy[Title/Abstract]) OR therapies[Title/Abstract]) OR therapeutic[Title/Abstract]) OR monotherap*[Title/Abstract]) OR polytherap*[Title/Abstract]) OR pharmacotherap*[Title/Abstract]) OR effect*[Title/Abstract]) OR efficacy[Title/Abstract]) OR treating[Title/Abstract]) OR treated[Title/Abstract]) OR management[Title/Abstract]) OR treat*[Title/Abstract]
4	(#2) AND #3
5	(#1) OR #4
6	(Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp])
7	(((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))
8	(#6) OR #7
9	(#5) AND #8
10	(#9) AND ("2015/10/09"[PDAT] : "2016/07/14"[PDAT])

Leitlinien in Medline (PubMed) am 14.07.2016

#	Suchfrage
1	arthritis, rheumatoid[MeSH Terms]
2	rheumatoid arthritis[Title]
3	(#1) OR #2
4	((((Guideline[Publication Type]) OR Practice Guideline[Publication Type]) OR Consensus Development Conference[Publication Type]) OR Consensus Development Conference, NIH[Publication Type]) OR guideline*[Title]
5	(#3) AND #4
6	(#5) AND ("2015/10/09"[PDAT] : "2016/07/14"[PDAT])

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