Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: rheumatoide Arthritis

Stand: September 2017

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Behandlung der 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 IQWiG-Beauftragung zu Nutzenbewertung von biotechnologisch hergestellten Wirkstoffen zur Behandlung der rheumatoiden Arthritis ; Vorläufiger Bericht A16-70 veröffentlicht am 01.03.2017
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)
Rheumatoide 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 […]
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 […]
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, […]
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 (…) […]
Prednison H02AB07 (z.B. Prednison-ratiopharm®)	ist angezeigt zur Behandlung von Erkrankungen, die einer systemischen Therapie mit Glucocorticoiden bedürfen. Hierzu gehören je nach Erscheinungsform und Schweregrad: **Rheumatologie:** - […] - Aktive rheumatoide Arthritis (…) mit schweren progredienten Verlaufsformen, z. B. schnell destruierend verlaufende Form (…)

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	und/oder extraartikuläre Manifestationen (…) […]
Klassische (synthetische) DMARDs (Basistherapeutika)	
Chloroquinphosphat P01BA01 Resochin®	Chronische Polyarthritis (rheumatoide Arthritis) einschließlich juveniler chronischer Arthritis. […] (Stand: Juli 2016)
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 generisch	Azathioprin Heumann ist bei Patienten mit nachfolgend genannten Erkrankungen angezeigt, wenn Glukokortikosteroide nicht vertragen werden bzw. wenn mit hohen Dosen von Glukokortikosteroiden keine ausreichende therapeutische Wirkung erzielt werden kann: - Schwere Formen der aktiven rheumatoiden Arthritis (chronische Polyarthritis), die mit weniger toxischen, antirheumatischen Basis-Therapeutika (disease modifying anti-rheumatic drugs – DMARDs) nicht kontrolliert werden können […] (Stand: August 2016)
Ciclosporin L04AD01	Rheumatoide Arthritis: Behandlung von schwerer, aktiver rheumatoider Arthritis. […] (Stand: Dezember 2015)

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Deximune®	
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: September 2016)

II. Zugelassene Arzneimittel im Anwendungsgebiet	
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 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: Juni 2016)
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: Juni 2016)

II. Zugelassene Arzneimittel im Anwendungsgebiet

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 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 2016)
Baricitinib L04AA37 Olumiant®	*JAK1/JAK2-Inhibitor* Olumiant ist angezeigt zur Behandlung von mittelschwerer bis schwerer aktiver rheumatoider Arthritis bei erwachsenen Patienten, die auf eine vorangegangene Behandlung mit einem oder mehreren krankheitsmodifizierenden Antirheumatika (DMARDs) unzureichend angesprochen oder diese nicht vertragen haben. Olumiant kann als Monotherapie oder in Kombination mit Methotrexat eingesetzt

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	werden. (Stand: Februar 2017)
Tofacitinib L04AA29 Xeljanz®	*JAK1/JAK2-Inhibitor* XELJANZ ist in Kombination mit Methotrexat (MTX) indiziert zur Behandlung der mittelschweren bis schweren aktiven rheumatoiden Arthritis (RA) bei erwachsenen Patienten, die auf ein oder mehrere krankheitsmodifizierende antirheumatische Arzneimittel unzureichend angesprochen oder diese nicht vertragen haben. XELJANZ kann als Monotherapie gegeben werden, wenn MTX nicht vertragen wird oder wenn eine Behandlung mit MTX ungeeignet ist.(Stand: März 2017)
Sarilumab L04AC14 Kefzara®	*IL-6-Antagonist* Kevzara ist in Kombination mit Methotrexat (MTX) indiziert zur Behandlung der mittelschweren bis schweren aktiven rheumatoiden Arthritis (RA) bei erwachsenen Patienten, die auf ein oder mehrere krankheitsmodifizierende antirheumatische Arzneimittel (DMARDs) unzureichend angesprochen oder diese nicht vertragen haben. Kevzara kann als Monotherapie gegeben werden, wenn MTX nicht vertragen wird oder wenn eine Behandlung mit MTX ungeeignet ist. (Stand: August 2017)

Quellen: Lauer-Fischer; AMIS; Fachinformation

Gemeinsamer Bundesausschuss

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

Inhalt

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und evidenzbasierten systematischen Leitlinien zur Indikation rheumatoide Arthritis durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 19.12.2016 abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, Clinical Evidence, DAHTA, G-BA, GIN, IQWiG, NGC, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 1105 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Zusätzlich wurde die

Referenz „Vorläufiger Berichtsplan; Auftrag A16-70“ des IQWiG am 04.05.2017 aufgenommen. Insgesamt ergab dies 35 Quellen, die in die synoptische Evidenzübersicht aufgenommen wurden.

Indikation:

Erwachsenen Patientinnen und Patienten mit mittelschwerer bis schwerer aktiver rheumatoider Arthritis, die unzureichend auf eine vorangegangene Behandlung mit einem oder mehreren krankheitsmodifizierenden Antirheumatika (DMARDs) angesprochen oder diese nicht vertragen haben. (Monotherapie oder in Kombination mit Methotrexat)

Abkürzungen

ACR	American College of Rheumatology
AE	adverse event
AHRQ	Agency for Health Research and Quality
AIMS	Abatacept in Inadequate responders to Methotrexate
Anti-CCP-Ak	Antikörper gegen zyklisch citrullinierte Peptide
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
bDMARD	Biological DMARD (Biologika oder biologische DMARD)
BSR	British Society for Rheumatology
CI	confidence intervall
CrI	credible interval
CRP	C-reactive protein
csDMARD	Conventional synthetic DMARD (konventionelle synthetische DMARD)
DAHTA	Deutsche Agentur für Health Technology Assessment
DAS	Disease Activity Score
DAS28	Disease Activity Score 28
DMARD	Disease modifying anti-rheumatic drug
ES	Erosion Score
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of recommendation
HAQ	Health Assessment Questionnaire
HD	high dose
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
IR	inadaequate response
KQ	key question
LD	low dose
LEF	Leflunomid
LoA	Level of Agreeement
MTC	Mixed-treatment comparisons

MTX	Methotrexate
NGC	National Guideline Clearinghouse
NICE	National Institute for Health and Care Excellence
NNTB	number needed to treat for an additional beneficial outcome
RA	rheumatoid arthritis
RCT	Randomized controlled trial
RR	risk ratio
SAE	serious adverse event
SASP	Sulfasalazine
SD	standard deviation
SD	standard dose
SF-36	Short Form 36
SIGN	Scottish Intercollegiate Guidelines Network
SSZ	sulfasalazine
TNF	tumour necrosis factor
TRIP	Turn Research into Practice Database
tsDMARD	Targeted synthetic DMARD (zielgerichtete synthetische DMARD)

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG), 2017 [12]. Biotechnologisch hergestellte Wirkstoffe bei rheumatoider Arthritis; Vorläufiger Berichtsplan; Auftrag A16-70	**2 Fragestellung** Das Ziel der vorliegenden Untersuchung ist • die Nutzenbewertung von Biologika im Vergleich untereinander bei Patienten mit rheumatoider Arthritis hinsichtlich patientenrelevanter Endpunkte. **3 Projektverlauf** 3.1 Zeitlicher Verlauf des Projekts Der Gemeinsame Bundesausschuss (G-BA) hat am 24.11.2016 das IQWiG mit der Bewertung von Biologika zur Behandlung der rheumatoiden Arthritis beauftragt. … **4 Methoden** 4.1 Kriterien für den Einschluss von Studien in die Untersuchung *4.1.1 Population* Für die Nutzenbewertung werden Studien mit Erwachsenen (Patienten ≥ 18 Jahre) mit rheumatoider Arthritis berücksichtigt. Es werden sowohl Studien eingeschlossen, in denen Patienten eine Erstlinientherapie erhalten haben, als auch Studien, in denen Patienten weitere Therapielinien erhalten haben. *4.1.2 Prüf- und Vergleichsintervention* Alle Biologika sollen untereinander verglichen werden und sind damit sowohl Prüf- als auch Vergleichsintervention. Zum Zeitpunkt der Erstellung des vorläufigen Berichtsplans sind dies die Biologika (Handelsname): • Abatacept (Orencia) • Adalimumab (Humira) • Anakinra (Kineret) • Certolizumab Pegol (Cimzia) • Etanercept (Enbrel, Benepali[2]) • Golimumab (Simponi) • Infliximab (Remicade, Flixabi[2], Inflectra[2], Remsima[2]) • Rituximab (MabThera) • Tocilizumab (RoActemra) Um die Biologika innerhalb einer gemeinsamen Analyse auch indirekt untereinander vergleichen zu können, werden neben Studien, die 2 Biologika direkt untereinander vergleichen, auch Studien in die Nutzenbewertung eingeschlossen, die Biologika mit einem möglichen Brückenkomparator vergleichen. Als mögliche Brückenkomparatoren kommen Brückenkomparatoren 1. Grades infrage. Ein

	Brückenkomparator 1. Grades ist eine Intervention (inklusive Placebo), für die ein direkter Vergleich sowohl zu einer Prüf- / Vergleichsintervention als auch in einer weiteren Studie zu einer anderen Prüf- / Vergleichsintervention vorliegt. Ein solcher Brückenkomparator leistet damit einen Beitrag zur Bildung eines Netzwerkes für einen indirekten Vergleich. Die konkrete Festlegung von Brückenkomparatoren, die für die Nutzenbewertung herangezogen werden, kann daher erst anhand des Studienpools erfolgen. … [2] Biosimilar
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG), 2016 [13]. Systematische Leitlinienrecherche und -bewertung sowie Extraktion relevanter Empfehlungen für ein DMP Rheumatoide Arthritis	**3 Methoden** … Die Leitlinienempfehlungen und die Definitionen des Erkrankungsbilds wurden in einer strukturierten Informationssynthese inhaltlich zusammengefasst. Sofern dies inhaltlich sachgerecht möglich war, wurden Einzelempfehlungen zu übergreifenden Themenaspekten gemeinsam dargestellt und hinsichtlich der DMP-Relevanz bewertet. Zur Einschätzung der Relevanz von Empfehlungen zu einem Themenaspekt für ein DMP Rheumatoide Arthritis wurde der dazugehörige GoR und, wenn dieser nicht angegeben war, alternativ der LoE herangezogen: • Eine DMP-Relevanz wurde festgestellt, wenn von verschiedenen Leitlinien zu einem Themenaspekt inhaltlich konsistente Empfehlungen mit mehrheitlich hohem GoR oder alternativ mehrheitlich hohem LoE vorlagen. • … **4 Ergebnisse** … Die systematische Recherche im Internet erfolgte im November 2014 und die Nachrecherche im Zeitraum Oktober 2015 bis November 2015. Sie ergab nach Titel- und Abstractscreening 96 potenziell relevante Dokumente, die im Volltext gesichtet wurden. Nach Prüfung der Kriterien für den Leitlinieneinschluss konnten 18 relevante Leitlinien eingeschlossen werden. … **4.4.4.2 Medikamentöse Therapie (hier nur DMP-relevante Themen)** … ***Behandlungsziel*** 6 Leitlinien weisen als Therapieziel für die Behandlung mit DMARD von Patienten mit RA die Remission oder Erreichung einer niedrigen Krankheitsaktivität aus und empfehlen einen möglichst frühen Beginn der Therapie nach Diagnosestellung (Empfehlungen DMP-relevant). **Monotherapie** 6 Leitlinien empfehlen den Einsatz von csDMARD zur Initialtherapie bei rheumatoider Arthritis. Dabei wird Methotrexat[2] (MTX) als Mittel der

	ersten Wahl genannt. Bei MTX-Kontraindikationen oder Unverträglichkeiten werden in 2 Leitlinien alternativ auch Sulfasalazin oder Leflunomid zur Initialtherapie empfohlen, eine weitere Leitlinie nennt neben MTX auch Sulfasalazin als Mittel der Wahl (Empfehlungen DMP-relevant). [2] Nicht alle Methotrexat-Präparate haben eine Zulassung zur Behandlung von RA beziehungsweise es hat nur ein Teil der pharmazeutischen Unternehmen eine Zulassung für alle Darreichungsformen für die Indikation rheumatoide Arthritis (siehe exemplarisch [30-32]). 30. Medac. Methotrexat 5 Injektionslösung medac: Fachinformation [online]. 01.2015 [Zugriff: 13.07.2015]. URL: http://www.fachinfo.de/. 31. Pfizer. Lantarel FS 7,5/10/15/20/25 mg Fertigspritze: Fachinformation [online]. 01.2014 [Zugriff: 13.07.2015]. URL: http://www.fachinfo.de/. 32. Pfizer. Methotrexat „Lederle“ Lösung 25 mg/- 50 mg: Fachinformation [online]. 01.2014 [Zugriff: 13.07.2015]. URL: http://www.fachinfo.de/. 2 Leitlinien empfehlen bis zum Eintritt der Wirkung der Initialtherapie (Mono- oder in Kombination) die additive Gabe von Glukokortikoiden. In Abhängigkeit von der klinischen Symptomatik sollten die Glukokortikoide aber so schnell wie möglich wieder ausgeschlichen werden (Empfehlungen DMP-relevant). **Kombinationstherapie mehrerer csDMARD** 2 Leitlinien empfehlen eine Kombinationstherapie[3] von csDMARD, wenn eine Monotherapie nicht zielführend ist. Eines der csDMARD sollte dabei Methotrexat[2] sein, jedoch nur wenn keine Kontraindikationen vorliegen (Empfehlungen DMP-relevant). 4 Leitlinien geben bei Patienten, die nicht angemessen auf die Initialtherapie (Monotherapie) ansprechen, der Kombinationstherapie[3] mit csDMARD den Vorzug. Dabei verweist 1 Leitlinie auch auf den Vorzug vor einer sequenziellen Monotherapie (Empfehlung DMP-relevant). [3] Es ist im Einzelfall zu prüfen, ob die Medikamente auch für die in den Leitlinien jeweils genannten Kombinationstherapien zugelassen sind. Nach Information aus einer Stellungnahme zum Vorbericht ist in Deutschland für die Kombination mit bDMARD nur MTX zugelassen. **Kombinationstherapie csDMARD und bDMARD** 5 Leitlinien empfehlen bei unzureichendem Ansprechen einer csDMARD-Therapie (Mono- oder Kombinationstherapie) eine Kombination[3] aus csDMARD und biologischen DMARD (bDMARD). Die Indikationsstellung sollte durch einen Rheumatologen erfolgen. 2 Leitlinien empfehlen explizit die Kombination von Methotrexat[2] und einem Biologikum (Empfehlungen sind DMP-relevant). **Therapie mit bDMARD**

	3 Leitlinien empfehlen, die Therapie von TNF-α-Antagonisten auf Biologika mit anderen Wirkmechanismen oder andere TNF-α-Antagonisten umzustellen, wenn die Wirksamkeit ausbleibt oder die Behandlung wegen Nebenwirkungen abgebrochen werden muss (Empfehlungen DMP-relevant). 2 Leitlinien geben Empfehlungen zur Behandlung mit Rituximab[5]. Rituximab wird für Patienten mit Kontraindikationen gegen TNF-α-Antagonisten und für Patienten mit hoher Krankheitsaktivität, bei denen die Behandlung mit einem oder mehreren Biologika erfolglos geblieben ist, empfohlen. 1 Leitlinie weist auf die besondere Effektivität von Rituximab bei Patienten mit positivem Rheumafaktor oder positivem Anti-CCP-Ak-Wert hin (Empfehlungen DMP-relevant). [5] Gemäß Fachinformation ist Rituximab in Deutschland nur in der intravenösen Darreichungsform für den Anwendungsbereich rheumatoide Arthritis zugelassen [35]. 35. Roche. MabThera i.v.: Fachinformation [online]. 05.2014 [Zugriff: 15.07.2015]. URL: http://www.fachinfo.de/. **Analgetika (reine Schmerzmittel)** 2 Leitlinien empfehlen bei unzureichender Schmerzkontrolle die Gabe von Analgetika. Dabei werden von den jeweiligen Leitlinien unterschiedliche Präparate genannt. 1 Leitlinie gibt dabei die Empfehlung, dass durch den Einsatz von Analgetika eine Langzeittherapie mit NSAR oder COX-2-Antagonisten verhindert beziehungsweise verkürzt werden kann (Empfehlungen DMP-relevant). …
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG), 2013 [11]. 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 bio-technologisch 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

<u>*Hinweis*</u>: 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 gesund-heitsbezogenen 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.

Cochrane Reviews

Singh JA et al., 2016 [28]. Biologic or tofacitinib monotherapy for rheumatoid arthritis in people with traditional disease-modifying anti-rheumatic drug (DMARD) failure: a Cochrane Systematic Review and network meta-analysis (NMA)	1. Fragestellung To assess the benefits and harms of biologic monotherapy (includes anti-tumor necrosis factor (TNF) (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab) or non-TNF (abatacept, anakinra, rituximab, tocilizumab)) or tofacitinib monotherapy (oral small molecule) versus comparator (placebo or MTX/other DMARDs) in adults with RA who were MTX/other DMARD-experienced.
	2. Methodik Population: Adults, 18 years or older, with RA, MTX/other DMARD-experienced, i.e., whose treatment with MTX/other DMARDs had failed due to any reason including incomplete response, intolerance or adverse events to MTX/other DMARDs Intervention/ Komparator: Biologics (abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab) or tofacitinib used alone that is,monotherapy (used without MTX and other traditional DMARDs), compared to placebo plus traditional DMARDs (including methotrexate (MTX)) or combinations of DMARDs or placebo alone or to biologics. Endpunkte: ACR50, RA disease remission (disease activity score (DAS) < 1.6 or DAS28 < 2.6), 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: Aktualisierung bis Juni 2015 Anzahl eingeschlossene Studien/Patienten (Gesamt): update includes 40 new RCTs for a total of 46 RCTs, of which 41 studies with 14 049 participants provided data Qualitätsbewertung der Studien: Cochrane 'Risk of bias' tool & GRADE approach for both direct and NMA estimates.
	3. Ergebnisdarstellung comparator was • placebo in 16 RCTs (4 532 patients), • MTX or other DMARD in 13 RCTs (5 602 patients), and • another biologic in 12 RCTs (3 915 patients) <u>Qualität der Studien:</u> reasonably good, poor reporting of the conduct of the included trials, only 37% of included trials reporting adequate sequence generation, 37%of trials judged to be at low risk for allocation concealment,

	selective reporting bias could not be assessed since for several (89%) trials, as we could not find published protocols **Monotherapy versus placebo** ACR50 • Direct evidence (moderate quality → downgraded for inconsistency): clinically meaningful and statistically significant improvement versus placebo, RR 4.68 (95% CI, 2.93 to 7.48); absolute benefit 23% (95% CI, 18% to 29%), NNTB = 5 (95% CI, 3 to 8) HAQ • Direct evidence (moderate quality → downgraded for inconsistency): clinically meaningful and statistically significant improvement versus placebo, with a MD of -0.32 (95% CI, -0.42 to -0.23); absolute benefit of -10.7% (95% CI, -14% to -7.7%), NNTB = 4 (95% CI, 3 to 5) Remission in RA (DAS) • Direct evidence (moderate quality → downgraded for imprecision): clinically meaningful and statistically significant greater proportion of participants achieving remission in RA versus placebo, with RR 1.12 (95% CI, 1.03 to 1.22); absolute benefit 10% (95% CI, 3% to 17%); NNTB = 10 (95% CI, 8 to 21) Withdrawals due to adverse events (WdAE) • Direct evidence (low quality → downgraded for imprecision and inconsistency): results compared to placebo inconclusive, with wide confidence intervals encompassing the null effect and evidence of an important increase Serious adverse events (SAE) • Direct evidence (low quality → downgraded for serious imprecision): results compared to placebo inconclusive, with wide confidence intervals that included the null effect and the evidence of an important increase Cancer • no data available for cancer for monotherapy vs. placebo **Monotherapy versus active comparator (MTX/other DMARDs)** ACR50 • clinically meaningful and statistically significant improvement compared to active comparator (MTX/other DMARDs), RR 1.54 (95% CI, 1.14 to 2.08); absolute benefit 13% (95% CI, 2% to 23%), NNTB = 7 (95% CI, 4 to 26) • TNF biologic monotherapy showed a statistically significant improvement with RR of 1.43 (95% CI, 1.06 to1.93) versus MTX/other DMARDs; • non-TNF monotherapy was not significant (RR: 1.57 (95% CI, 0.67 to 3.68))

	Function assessed by HAQ • clinically meaningful and statistically significant improvement versus active comparator (MTX/other DMARDs) with a MD of -0.27 (95% CI, -0.40 to -0.14); absolute benefit of -9% (95% CI, -13.3% to -4.7%), NNTB = 2 (95% CI, 2 to 4) • Non-TNF biologic monotherapy showed a clinically meaningful and statistically significant MD for direct estimates versus the active comparator group (MTX/other DMARDs) • TNF biologic monotherapy did not show a clinically meaningful and statistically significant MD for direct estimates versus the active comparator • no differences in HAQ scores by the type of biologic (TNF versus non-TNF biologics) or receptor versus antibody TNF-biologic Remission in RA (DAS) • no clinically meaningful and statistically significant direct estimates for biologic monotherapy versus the active comparator group Withdrawals due to adverse events • results inconclusive when compared to the active comparator, with wide confidence intervals encompassing the null effect and evidence of an important increase Serious adverse events • results inconclusive, with wide confidence intervals that included the null effect and the evidence of an important increase when compared to the active comparator Cancer • Direct evidence (low quality → downgraded for serious imprecision): results for all cancer comparisons inconclusive, with wide confidence intervals • TNF biologics did not differ from non-TNF biologics in the risk of cancer • odds of cancer did not differ between SD, HD and LD biologic monotherapy
	4. Fazit der Autoren: Based mostly on RCTs of six to 12-month duration in people with RA who had previously experienced and failed treatment with MTX/other DMARDs, biologic monotherapy improved ACR50, function and RA remission rates compared to placebo or MTX/other DMARDs. Results were inconclusive for whether biologic monotherapy was associated with an increased risk of withdrawals due to adverse events, serious adverse events or cancer, versus placebo (no data on cancer) or MTX/other DMARDs. *5. Kommentar zum Review*

	• *Ergebnisse der NMA wegen unzureichender Beschreibung des Umgangs mit den zentralen Annahmen nicht dargestellt* • *„radiographic progression" nicht berichtet wegen fraglicher Patientenrelevanz*
Singh JA et al., 2016 [27]. 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 Population: Adults, 18 years or older, with RA who were MTX/DMARD-experienced (including MTX/DMARD- IR) Intervention / Komparator: Biologics (abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab) or tofacitinib 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. Endpunkte: 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: Aktualisierung 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 <u>Qualität der Studien:</u> 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%). **ACR50** • <u>Direct evidence</u> (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). **function measured by the HAQ** • 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). **remission in RA** • 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). **withdrawals due to adverse events** • 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). **serious adverse events** • 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%). **cancer** • 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.
	• 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. • *Kommentar zum Review* • *Ergebnisse der NMA wegen unzureichender Beschreibung des Umgangs mit den zentralen Annahmen nicht dargestellt* • *„radiographic progression" nicht berichtet wegen fraglicher Patientenrelevanz* • *Unklar wie moderate bis schwere Krankheitsaktivität als Einschlusskriterium definiert war.*
Hazlewood GS et al., 2016 [10]. Methotrexate monotherapy and methotrexate combination therapy with traditional and biologic disease modifying anti-rheumatic drugs for rheumatoid arthritis: A network meta-analysis siehe auch **Hazlewood GS et al., 2016 [9].**	1. Fragestellung To compare methotrexate and methotrexate-based DMARD combinations for rheumatoid arthritis in patients naïve to or with an inadequate response (IR) to methotrexate.
	2. Methodik Population: adults (age > 18 years) with RA Intervention/Komparator: methotrexate monotherapy or in combination with any currently used conventional synthetic DMARD , biologic DMARDs, or tofacitinib Endpunkte: • major outcomes (ACR50 response, radiographic progression and withdrawals due to adverse events) • multiple minor outcomes Suchzeitraum: Anzahl eingeschlossene Studien/Patienten (Gesamt): 158/about 37 000 Qualitätsbewertung der Studien: Cochrane Risk of Bias tool, trials at high risk of bias excluded from main analysis, quality of evidence evaluated by GRADE approach. Heterogeneity: explored through meta-regression and subgroup analyses
	3. Ergebnisdarstellung (heir die nur die Ergebnisse für die Subgruppe der „Methotrexate-inadequate patients" dargestellt **ACR50** • 45 trials with 12 549 patients included in analysis • no evidence for certolizumab found, as available trials were at high risk of bias Credible intervals in **pair wise comparisons** between different treatments combinations were wide, although some estimates reached statistical significance: • methotrexate + etanercept was superior to the combination of methotrexate + most biologic DMARDs, and

	• methotrexate + sulfasalazine + hydroxychloroquine was superior to methotrexate + the biologic DMARDs intravenous abatacept, infliximab, and tocilizumab 4 mg/kg The quality of evidence for methotrexate + sulfasalazine + hydroxychloroquine versus methotrexate was judged to 'moderate' as some minor inconsistencies existed in the findings of the two trials that compared triple therapy with MTX + etanercept (RACAT 2013; TEAR 2012), and because the study design of one of the trials was judged to indirectly address the comparison of interest (TEAR 2012). This trial randomised patients at baseline a step-up to triple therapy versus a step-up to methotrexate + etanercept, only if an inadequate response to methotrexate was found after 6 months (TEAR 2012). In the **methotrexate-inadequate response network** several treatments were statistically significantly superior to oral methotrexate for ACR50 response: • triple therapy (moderate quality evidence), • methotrexate + hydroxychloroquine (low quality evidence), • methotrexate + leflunomide (moderate quality evidence), • methotrexate + intramuscular gold (very low quality evidence), • methotrexate + most biologics (moderate to high quality evidence),and • methotrexate + tofacitinib (high quality evidence) There was a 61%probability of an ACR50 response with triple therapy, compared to a range of 27%to 64%for the combinations of methotrexate + biologic DMARDs that were statistically significantly superior to oral methotrexate. Methotrexate + cyclosporine and methotrexate + tocilizumab (8 mg/kg) had a statistically higher rate of withdrawals due to adverse events than oral methotrexate and methotrexate + abatacept had a statistically lower rate of withdrawals due to adverse events than several treatments.
	4. Fazit der Autoren We found moderate to high quality evidence that combination therapy with methotrexate + sulfasalazine+ hydroxychloroquine (triple therapy) or methotrexate + most biologic DMARDs or tofacitinib were similarly effective in controlling disease activity and generally well tolerated in methotrexate-naïve patients or after an inadequate response to methotrexate. Methotrexate + some biologic DMARDs were superior to methotrexate in preventing joint damage in methotrexate-naïve patients, but the magnitude of these effects was small over one year. *5. Kommentar zum Review* • *Unklar wie moderate bis schwere Krankheitsaktivität als Einschlusskriterium definiert war.* • *Bildegebende Befunde wegen fraglicher Patientenrelevanz nicht*

	dargestellt.
Lopez-Olivo MA et al., 2015 [15]. 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: 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
	1. 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. Kommentar zum Review*

	• *heterogene Patientenpopulation (in Bezug auf Vortherapien) eingeschlossen* • *Unklar wie moderate bis schwere Krankheitsaktivität als Einschlusskriterium definiert war.*
Ruiz GV et al., 2014 [22]. 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: searches updated from 2009 (date of last search for the original review) to 5 June 2014 Anzahl eingeschlossener Studien/Patienten (Gesamt): 11/k.A. Qualitätsbewertung der Studien: Cochrane Risk of Bias zur Bewertung des Verzerrungsrisikos auf Einzelstudienebene, GRADE zur Bewertung der overall quality of evidence
	3. Ergebnisdarstellung • duration of follow-up varied from 12 to 52 weeks • range of doses of certolizumab pegol varied from 50 to 400 mg given subcutaneously (sc) • control was placebo plus MTX in five trials and placebo in four trials **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 (10 Studien, n = 4324):** • 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 (10 Studien, n = 3711):** • 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. *5. Kommentar zum Review:* • *Unklar wie moderate bis schwere Krankheitsaktivität als Einschlusskriterium definiert war.*
Lethaby A et al., 2013 [14]. Etanercept for	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

the treatment of rheumatoid arthritis	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 vorbehandelt 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 <u>Primär</u>: 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. <u>Sekundär</u>: • 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). Suchzeitraum: 1966 bis 2003; 2003 bis 01/2012 (Update) Anzahl eingeschlossene Studien/Patienten (Gesamt): 9/2 800 Qualitätsbewertung der Studien: Cochrane Risk of Bias Tool Heterogenitätsanalysen: gemäß Cochrane Handbuch
	3. Ergebnisdarstellung <u>Allgemein:</u> 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: <u>ACR 50 (number of tender or swollen joints and other outcomes such as pain and disability)</u> - 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 <u>Disease activity</u> - 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.
	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. *5. Kommentar zum Review:* • *Ergebnisse zu Röntgenbefunden nicht extrahiert wegen fraglicher Patientenrelevanz.* • *Unklar wie moderate bis schwere Krankheitsaktivität als Einschlusskriterium definiert war.*

Systematische Reviews

Teitsma XM et al., 2016 [33]. Tocilizumab as monotherapy or combination therapy for treating active rheumatoid arthritis: a meta-analysis of efficacy and safety reported in randomized controlled trials siehe auch: **Navarro-Millan I et al., 2012 [19].** und **Schoels MM et al., 2013 [23].**	1. Fragestellung To evaluate the efficacy and safety in patients with RA of TCZ monotherapy versus add-on TCZ combination therapy, and both TCZ therapies versus continuing the current csDMARD therapy
	2. Methodik Population: Adult patients with rheumatoid arthritis. Intervention / Komparator: TCZ 8 mg/kg (TCZMONO) versus TCZ 8 mg/kg + csDMARD (TCZCOMBI) TCZMONO versus csDMARD or TCZCOMBI versus csDMARD Endpunkt: ACR 20/50/70 responses, Disease Activity Score in 28 joints (DAS28), incidence of AEs and serious AEs (SAEs) within≤52 weeks Suchzeitraum: bis Mai 2015 Anzahl eingeschlossene Studien/Patienten (Gesamt): 11 RCTs or quasi-RCTs/ 6 679 patients Qualitätsbewertung der Studien: Cochrane Collaboration recommendations for assessing risk of bias Heterogenitätsanalysen: I squared statistic calculated to quantify heterogeneity between studies. Publication bias: assessed by visual inspection of asymmetry in funnel plots
	3. Ergebnisdarstellung <u>Qualität der Studien</u> Generally, there was a low risk of selection bias because of adequate allocation concealment, except for the OPTION study. During the study selection we noticed large heterogeneity between studies; hence a random-effects model was applied. • no clear indication of publication bias, should be interpreted with caution in small number of trials <u>Wirksamkeit</u> **DAS28 < 2.6** In the TCZ monotherapy and combination strategy, pooled effect estimates for achieving remission were significantly higher compared to csDMARD therapy (RR 3.95; 95 % CI 2.23, 7.00, p < 0.001 and RR 8.77; 95 % CI 4.10, 18.75, p < 0.001, respectively).

	On comparison of the two TCZ strategies, the effect estimate was significantly higher for the combination strategy (RR 1.21; 95 % CI 1.09, 1.36, p < 0.001). **ACR20 response** Pooled effect estimates for achieving ACR20 response were significantly higher for both the TCZMONO (RR 1.68; 95 % CI 1.21, 2.32, p = 0.002) and TCZCOMBI (RR 2.10; 95 % CI 1.48, 2.99, p < 0.001) strategy, when compared to csDMARD therapy. There was no difference between the two TCZ strategies (p = 0.11). **ACR50 response** The proportion of ACR50 responders was statistically higher with both TCZ strategies compared to csDMARD therapy (TCZMONO: RR 1.87; 95 % CI 1.19, 2.95, p = 0.007 and TCZCOMBI: RR 3.00; 95 % CI 1.80, 4.99, p < 0.001). Patients treated with the add-on TCZCOMBI strategy achieved an ACR50 response significantly more often than with the TCZMONO strategy; however, this effect estimate was relatively small (RR 1.14; 95 % CI 1.03, 1.26, p = 0.008). **ACR70 response** The pooled effect estimates of ACR70 response rates were significantly higher in patients treated with the TCZMONO and TCZCOMBI strategy compared to patients treated with csDMARD therapy (RR 2.11; 95 % CI 1.18, 3.78, p = 0.01 and RR 5.32; 95 % CI 2.31, 12.25, p < 0.001, respectively). There was no statistically significant difference between the two TCZ strategies (p = 0.14). **Safety outcomes: Adverse events** For both TCZ strategies, the pooled risk estimates for experiencing one or more AE during treatment was significantly higher compared to csDMARD therapy (TCZMONO: RR 1.08; 95 % CI 1.01, 1.15, p = 0.03; TCZCOMBI: RR 1.12; 95 % CI 1.06, 1.18, p < 0.001). In the meta-analyses of TCZMONO versus TCZCOMBI, there was no statistically significant difference between the strategies (p = 0.17). SAEs occurred more frequently in the TCZMONO (RR 1.21; 95 % CI 0.87, 1.69) and TCZCOMBI (RR 1.21; 95 % CI 0.91, 1.60) strategy compared to csDMARD therapy. When comparing the incidence of SAEs with the TCZMONO and TCZCOMBI strategies, the pooled risk estimate was significantly higher with the combination strategy (RR 1.40; 95 % CI 1.03, 1.92, p = 0.03).
	4. Fazit der Autoren

	[…] the efficacy of TCZMONO is nearly equivalent to TCZCOMBI in the management of active RA. Although the effect estimate for achieving DAS28 < 2.6 and ACR50 response was significantly higher with the TCZCOMBI strategy, this is at the cost of a significant increase in the risk of SAEs when compared to TCZMONO. Thus, if patients do not achieve the treatment target after initiating csDMARD therapy because of intolerance, switching to TCZMONO is a feasible option in clinical practice, whereas similar efficacy can be expected compared to inadequate responders to csDMARDs who switch to add-on TCZCOMBI therapy. *Kommentar zu Review:* • *Tocilizumab hat Zulassung für „mäßige bis schwere RA“* • *Unklar wie moderate bis schwere Krankheitsaktivität als Einschlusskriterium definiert war.* • *Competing interests: All authors have participated in the U-Act-Early study [42] but have no non-financial competing interests. JWJB previously received research grants (to his department) and consultancy fees from AbbVie, BMS, Crescendo, MSD, Mundipharma, Pfizer, Roche, Sun and UCB.* *42. Bijlsma JW, et al. Early rheumatoid arthritis treated with tocilizumab, methotrexate, or their combination (U-Act-Early): a multicentre, randomised, double-blind, double dummy, strategy trial. Lancet. 2016;388(10042):343–55.*
Stevenson M et al., 2016 [32]. Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for the treatment of rheumatoid arthritis not previously treated with disease-modifying antirheumatic drugs and after the failure of conventional disease-modifying	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 Population: The three populations under consideration in this assessment were: i. Adults with severe active RA not previously treated with MTX (hier nicht berichtet) 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:

antirheumatic drugs only: systematic review and economic evaluation	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: 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: bis 2013 Anzahl eingeschlossene Studien/Patienten (Gesamt): 60/k.A. Qualitätsbewertung der Studien: NHS Centre for Reviews and Dissemination report and Cochrane Risk of Bias tool
	3. Ergebnisdarstellung 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. 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. Qualität der Studien: 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 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. *5. Kommentar zum Review* • *Ergebnisse des Reviews sind Grundlage für Aktualisierung der Leitlinie vom NICE (siehe unten)*
Conway R et al., 2016 [5].	1. Fragestellung To evaluate the relative risk (RR) of pulmonary disease among patients with

Leflunomide Use and Risk of Lung Disease in Rheumatoid Arthritis: A Systematic Literature Review and Metaanalysis of Randomized Controlled Trials	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 Anzahl eingeschlossene Studien/Patienten (Gesamt): 8/4 579 Qualität der Studien: Cochrane risk of bias tool Heterogenitätsanalysen: Random-effects metaanalysis using the Mantel-Haenszel method was used throughout because the I2 statistic revealed the presence of between-study heterogeneity Publication bias: funnel plots
	3. Ergebnisdarstellung • 2 274 received LEF and 2 305 received comparator treatments • 3 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 <u>Qualität der Studien:</u> data suggested a low risk of bias in the included studies, no evidence of publication bias • 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 (I2 = 88%) • 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. *5. Kommentar zum Review*

	• *Unklar wie moderate bis schwere Krankheitsaktivität als Einschlusskriterium definiert war.* • *Interessenkonflikte und Finanzierung unklar*
Singh JA et al., 2015 [26]. 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 Population: RA patients Intervention: biologics Komparator placebo, biologics, or traditional DMARDs or their combinations Endpunkte: malignancies Suchzeitraum: until 02/2014 Anzahl eingeschlossene Studien/Patienten (Gesamt): 106/42 330 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) o MTX-naïve (24 trials), o traditional DMARD-experienced (71 trials), and o anti-TNF biological drug-experienced (11 trials) pts **Serious infections** <u>Traditional Meta-analysis:</u> • a total of 525 serious infections among the 59 trials • involving 68 comparisons of standard-dose biologic +/− traditional DMARD (342 events) with traditional DMARD monotherapy (183 events) • 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 <u>Stratified analysis</u> A clinically important and statistically significantly higher risk of serious infections with biologic compared to traditional DMARDs was also seen in:

	• duration of follow-up 6-12 months; • biologic when used in combination with traditional DMARDs; • established RA (2 to 10 years of disease duration); • studies published between 2000 and 2004; • studies with a low risk of bias; and • when the comparator was traditional DMARD plus placebo
	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. *5. Kommentar zum Review* • *research funded by the rheumatology division at the University of Alabama at Birmingham, funders played no role in data collection, analysis, interpretation, writing of the manuscript and the decision to submit the manuscript for publication.* • *Ergebnisse der "Network MA" wegen fehlender Diskussion zu zentralen Annahmen nicht dargestellt.* • *Unklar wie moderate bis schwere Krankheitsaktivität als Einschlusskriterium definiert war.*
De Oliveira Costa J et al., 2015 [6]. 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/k.A. 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 • 9 trials classified as randomised, but only 2 reported methods of randomization • Jadad scale score generally good (ranging from moderate to high) • pharmaceutical industry funded 6 studies • potential source of bias in 3 trials, only 1 study classified as low risk of bias *Efficacy of infliximab vs control* <u>Patients with insufficient response to MTX (6 studies):</u> 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% *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 der Autroren 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. *5. Kommentar zum Review* • *Funding: National Counsel of Technological and Scientific Development R$ 95.567,16 (Conselho Nacional de DesenvolvimentoCientífico e Tecnológico – CNPq) (Public notice MS-SCTIE-DECIT/CNPq no. 69/201; Case no. 564778/2010-9).* • *Conflicts of interestThe authors declare no conflicts of interest.* • *Unklar wie moderate bis schwere Krankheitsaktivität als Einschlusskriterium definiert war.* • *Metaannalytische Ergebnisse wegen hoher Heterogenität der Studienergebnisse mit Vorsicht zu bewerten.*

Canadian Agency for Drugs and Technologies in Health, 2015 [2]. Biologic Switching for Patients with Rheumatoid Arthritis: A Review of Clinical Effectiveness, Safety, and Guidelines	1. Fragestellung 1. What is the clinical effectiveness and safety of switching biologics for adult patients with rheumatoid arthritis (RA)? 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: January 1, 2010 and November 10, 2015 Anzahl eingeschlossene Studien/Patienten (Gesamt): 17 publications met the inclusion criteria and were included in this report (5 SRs, 2 RCTs and 8 evidence-based guidelines) Qualitätsbewertung der Studien: Assessment of Multiple Systematic Reviews (AMSTAR) tool, Downs and Black instrument, and the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument; strengths and limitations of each included study described
	3. Ergebnisdarstellung **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. <u>What is the clinical effectiveness and safety of switching biologics for adult patients with RA?</u> **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.

	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) *5. Kommentar zum Review* • *Schwere der Krankheitsaktivität nicht explizit als Einschlusskriterium formuliert*
Zhang X et al., 2014 [35]. Tofacitinib for acute rheumatoid arthritis patients who have had an inadequate response to disease-modifying antirheumatic drug (DMARD): a systematic review and meta-analysis	1. Fragestellung The aim of this systematic review andmeta-analysis is to assess the efficacy and safety of tofacitinib, compared to placebo or other medications, for the treatment of patients with acute rheumatoid arthritis who have had an inadequate response to at least one DMARD.
	2. Methodik Population: patients with acute rheumatoid arthritis (RA) Intervention/Komparator: (1) tofacitinib combination therapy versus placebo; (2) tofacitinib monotherapy versus placebo; and (3) tofacitinib versus other medications Endpunkte: (1) primary outcomes: ACR20 at week 12, serious adverse effects (sAE); (2) secondary outcomes: ACR20 at week 24, Disease Active Score (DAS)28-3[C-reactive protein (CRP)] at week 12 and 24, Health Assessment Questionnaire Disability Index (HAQ DI) at weeks 12 and 24, and other adverse effects (oAE) Suchzeitraum: bis 10. Mai 2013 Anzahl eingeschlossene Studien/Patienten (Gesamt): 10/4 929 Qualitätsbewertung der Studien: GRADE Heterogenitätsanalysen: $\chi 2$ and I 2 tests used, heterogeneity considered significant if either $\chi 2$ P value is <0.10 or I 2 is >50 % Publication bias: Funnel plot
	3. Ergebnisdarstellung • 6 studies with unclear risk of bias for sequence allocation and concealment because of their insufficient reported information • 2 studies considered at high risk of bias for incomplete outcome data due to completion rates less than 80 % • 5 studies had inadequate information about the patients who failed a ≧20 % reduction from baseline being assigned to 5 or 10 mg tofacitinib groups

	• all studies sponsored by Pfizer (manufacturer of tofacitinib) • funnel plot of the sAEs with clear asymmetry, publication bias cannot be excluded **Efficacy of tofacitinib + background therapy versus placebo + background therapy** • pooled analysis of six studies • tofacitinib had a superior effect over placebo (both with background therapy) at weeks 12 and 24 with significant heterogeneity **Efficacy of tofacitinib monotherapy versus placebo** • pooled results of three studies • tofacitinib monotherapy had a significantly greater effect over placebo • compared to adalimumab, tofacitinib was found to be more efficacious as well **Efficacy of tofacitinib + MTX versus adalimumab + MTX** • only two studies investigating tofacitinib compared with adalimumab, with one of these comparisons having combination therapy with another medication, pooled analysis not appropriate **Safety** • tofacitinib monotherapy had less serious adverse events (sAE) than placebo but not other adverse effects (oAE) • comparison of tofacitinib and placebo both with background therapy: no difference in sAE and oAE
	4. Anmerkungen/Fazit der Autoren Tofacitinib alone, or together with non-biologic DMARDs, was associated with more favorable remission in the signs and symptoms of RA than adalimumab or placebo. Also, tofacitinib monotherapy was safer than placebo with regards to reported sAE, but not oAE. However, the quality of evidence is exceedingly low; long-term, large-scale, and high quality post-marketing research is suggested to further verify the conclusion. *5. Kommentar zu Review:* • *Tofacitinib nur bei mittelschwerer bis schwerer aktiver RA zugelassen* • *Empfohlene Dosierung: 2mal 5mg pro Tag* • *Disclosures: None* • *Keine Info zur Finanzierung*
Song GG et al., 2014 [31]. Efficacy and safety of tofacitinib for active	1. Fragestellung The aim of this study was to assess the efficacy and safety of tofacitinib (5 and 10 mg twice daily) in patients with active rheumatoid arthritis (RA).
	2. Methodik Population: patients with active RA that had inadequately responded to

rheumatoid arthritis with an inadequate response to methotrexate or disease-modifying antirheumatic drugs: a meta-analysis of randomized controlled trials	DMARDs or MTX Intervention: tofacitinib Komparator: placebo Endpunkt: (1) number of patients who achieved an ACR 20% response rate (ACR20); (2) number of tender and swollen joints; (3) pain (visual analog scale); (4) patients' and physicians' global assessments of disease activity; (5) health assessment questionnaire (HAQ) score; and (6) C-reactive protein level. The safety outcomes were the number of patients who withdrew from the study because of adverse events (AEs), serious AEs, serious infections that were considered to be related to the medication, total number of infections, and abnormal liver function test results. Suchzeitraum: up to February 2013 Anzahl eingeschlossene Studien/Patienten (Gesamt): 5/1 590 Qualitätsbewertung der Studien: Jadad scores
	3. Ergebnisdarstellung • three phase-II and two phase-III trials • phase-II RCTs included 452 patients with RA (144 patients randomized to 5 mg of tofacitinib twice daily, 156 patients randomized to 10 mg of tofacitinib twice daily, and 152 patients randomized to placebo) who were included in this meta-analysis (hier nicht berichtet) • results of two phase-III trials (1 123 patients) confirmed findings in the phase-II studies (qualitative Beschreibung hier berichtet) **Phase-III-Studien** Van Vollenhoven et al. [10] performed a study in which 513 patients with an incomplete response to MTX were randomly assigned to 5 mg of tofacitinib twice daily, 10 mg of tofacitinib twice daily, or placebo for 12 months. Fleischmann et al. [11] performed a phase-III, double-blind, placebo-controlled, parallel-group, 6-month study in which 610 patients were randomly assigned in a 4:4:1:1 ratio to 5 mg of tofacitinib twice daily, 10 mg of tofacitinib twice daily, placebo for 3 months followed by 5 mg of tofacitinib twice daily, or placebo for 3 months followed by 10 mg of tofacitinib twice daily. Taken together, the findings in both of the phase-III trials (1,123 patients) confirmed the results of the meta-analysis of the phase-II RCTs of tofacitinib and showed that tofacitinib at dosages of 5 and 10 mg twice per day provided a clinical benefit in trials of patients with active RA with or without background MTX treatment. The phase-III RCTs revealed the need for studies on the safety of tofacitinib involving larger numbers of patients for longer periods.

	4. Anmerkungen/Fazit der Autoren Tofacitinib at dosages of 5 and 10 mg twice daily was found to be effective in patients with active RA that inadequately responded to methotrexate or disease-modifying antirheumatic drugs, and showed a manageable safety profile. *5. Kommentar zu Review* • *Tofacitinib nur bei mittelschwerer bis schwerer aktiver RA zugelassen* • *No potential conflict of interest relevant to this article was reported.* • *study supported by a grant from the Korea Healthcare Technology R&D Project, Ministry of Health and Welfare, Republic of Korea (A102065)*
Scott DL et al., 2014 [24]. 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 and associated systematic reviews	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 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 Komparator: DMARD monotherapy Endpunkte: American College of Rheumatology responses, withdrawals (for inefficacy), diability (HAQ score) Suchzeitraum: 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:
	3. Ergebnisdarstellung (hier nur „established“ berichtet) 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 ($p = 0.06$). **SR of established RA:** • 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 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. *5. Kommentar zum Review* • *Unklar wie moderate bis schwere Krankheitsaktivität als Einschlusskriterium definiert war.* • *vom NHS finanziert*
Michaud TL et al., 2014 [17].	1. Fragestellung To evaluate and update the safety data from RCTs of TNF inhibitors in

The Comparative Safety of Tumor Necrosis Factor Inhibitors in Rheumatoid Arthritis: A Meta-analysis Update of 44 Trials	patients treated for rheumatoid arthritis
	2. Methodik Population: > 18 year old RA patients Intervention: 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 • malignancies Suchzeitraum: 05/2013 Anzahl eingeschlossene Studien/Patienten (Gesamt): 44/11 700 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). o 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) o adalimumab: OR 1.69, 95% CI 1.12-2.54 →sig. difference o certolizumab pegol: OR 1.98, 95%CI 0.99-3.96 → n.s. o infliximab: OR 1.63, 95%CI 1.07-2.47 →sig. difference o golimumab OR 1.55, 95% CI 0.76-3.17 → n.s. o 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) o adalimumab: OR 1.38, 95%CI 1.00; 1.69 →sig. difference o certolizumab pegol: 1.67, 95%CI 1.09; 2.54 →sig. difference o infliximab 2.04, 95%CI 1.46; 2.84 →sig. difference o 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. Kommentar zum Review* • *Untersuchte Wirkstoffe nur für mittelschwere bis schwere RA zugelassen, Operationalisierung bei Einschluss unklar* • *research supported by the National Institutes of Health (RC1AR058601)* • *Conflict of Interest: None.*
Pierreisnard A et al., 2013 [21]. Meta-analysis of clinical and radiological efficacy of biologics in rheumatoid arthritis patients naive or inadequately responsive to methotrexate	1. Fragestellung To perform a metaanalysis of all available biologics in two patient populations that reflect clinical practice, namely, patients naive to methotrexate therapy (naive group) and patients with an inadequate response to methotrexate therapy.
	2. Methodik Population: adults with established RA, methotrexate-naive or unresponsive patients Intervention / Komparator: biologic-methotrexate therapy (five TNF-alpha antagonists, rituximab, abatacept and tocilizumab used with methotrexate) compared to placebo-methotrexate therapy (five TNF-alpha antagonists, rituximab, abatacept and tocilizumab used with methotrexate) Endpunkt: Primary clinical endpoint: ACR50 response rate • Primary radiological endpoint: absence of radiographic progression, defined as a modified total Sharp score (mTSS) changeno greater than 0.5 after 1 year. • Secondary endpoints: ACR20 response rate, the remission rate with remission defined as a 28-joint Disease Activity Score (DAS28) < 2.6, the low DAS28 rate (LDAS), defined as DAS28 < 3.2, mean structural disease progression as assessed by the mean mTSS change from baseline, and the number needed to treat (NNT) to obtain one ACR50 responder Suchzeitraum: Januar 1990 bis Februar 2013 Anzahl eingeschlossene Studien/Patienten (Gesamt): 22/11 374

	Qualitätsbewertung der Studien: Jadad score Heterogenitätsanalysen: Q test, using a significance level of 0.05, and reported with the I2 statistic (for which higher values indicate greater heterogeneity)
	3. Ergebnisdarstellung (hier nur „methotrexate-unresponsive patients“ berichtet) <u>Qualität der Studien:</u> The Jadad score was 3 or 4 for all 22 studies. Anzahl der Studien in den Subgruppen: 15 studies involved methotrexate-unresponsive patients. <u>Wirksamkeit</u> Hinweis: Number needed to treat-Ergebnisse und sekundäre Endpuntke wurden nicht dargestellt. **ACR50 response rate** • Biologics with methotrexate showed better efficacy than methotrexate alone (OR: 4.82; 95%CI: 3.83–6.08; P < 10−5). High heterogeneity was observed (I2 = 59%). **Rate of patients without modified total Sharp score (mTSS) progression at 1 year (1 study)** • Tocilizumab plus methotrexate showed better efficacy than methotrexate alone (OR: 2.87; 95%CI: 2.13–3.87; P < 10^{-4}).
	4. Fazit der Autoren: […] biologics combined with methotrexate are more effective than methotrexate alone in patients with RA. … In inadequate responders to methotrexate, biologic therapy with methotrexate showed greater clinical efficacy than methotrexate alone, with no significant difference across biologics. *5. Kommentar zum Review* • *Untersuchte Wirkstoffe nur für mittelschwere bis schwere RA zugelassen, Operationalisierung bei Einschluss unklar* • *Disclosure of interest: A. Pierreisnard, N. Issa: Abbott France organized a metaanalysis methods workshop but played no further role in the project. T. Barnetche received honoraria from Abbott and Roche. C. Richez received honoraria and a research grant from Abbott; Bristol-Myers Squibb; Nordic Pharma; Pfizer; Roche Chugai; Shering Plough; and Wyeth. T. Schaeverbeke received honoraria and a research grant from Abbott; Bristol- Myers Squibb; Nordic Pharma; Pfizer; Roche Chugai; Shering Plough; and Wyeth* • *Finanzierung unklar*

Thaler KJ et al., 2012 [34]. Drug Class Review: Targeted Immune Modulators: Final Update 3 Report	1. Fragestellung We systematically compared the efficacy, effectiveness, and safety (adverse events) of abatacept, adalimumab, alefacept, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, natalizumab, rituximab, tocilizumab, and ustekinumab in patients with rheumatoid arthritis (and other diseases).
	2. Methodik Population: RA and other diseases (e.g. ankylosing spondylitis) Intervention: Targeted Immune Modulators: abatacept, adalimumab, alefacept, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, natalizumab, rituximab, tocilizumab, and ustekinumab Komparator: Head-to-head evidence and placebo-controlled trials Endpunkt: radiological changes (for head-to-head trials), quality of life, functional capacity, alleviation of symptoms, hospitalizations, or mortality. Suchzeitraum: 2009 (January) to 2011 (October) *Hinweis: Es handelt sich um ein Update, allerdings werden ältere Ergebnisse auch kurz berichtet.* Anzahl eingeschlossene Studien/Patienten (Gesamt): 16 trials, 21 systematic reviews and meta-analyses, and seven observational studies for RA efficacy (Key Question 1). Für Key Question 2 war 1 RCT relevant. Qualitätsbewertung der Studien: Predefined criteria developed by the US Preventive Services Task Force (ratings: good, fair, poor) and the National Health Service Center for Reviews and Dissemination. We graded strength of evidence based on the methods guidance established for the Evidence-based Practice Center program of the Agency for Healthcare Research and Quality.
	3. Ergebnisdarstellung Qualität der Studien: Trials that had a fatal flaw in one or more categories were rated poor quality and not included in the analysis of the evidence report; trials that met all criteria were rated good quality. The majority of trials received a quality rating of fair. **Key Question 1. Efficacy and Effectiveness - RA** • 1 fair head-to-head RCT: Abatacept vs. infliximab → kein Unterschied nach 6 Monaten, nach einem Jahr war Abatacept signifikant wirksamer in folgenden Outcomes: ACR20/50 und Lebensqualität (SF-36). • Indirect comparisons of placebo-controlled randomized controlled trials with MTX combination therapy (based in metaregression) suggest that etanercept is statistically significantly more efficacious (ACR50) than abatacept, anakinra, infliximab, and tocilizumab (range of relative risks

	from 2.31 to 3.30). No statistically significant differences (ACR50) in efficacy could be detected among adalimumab, anakinra, infliximab, and tocilizumab.
	• Übersicht Meta-Analysen und ältere RCTs:
	  ○ Abatacept: 1 Meta-Analyse mit 7 RCTs zeigte signifikant bessere ACR50 response rates after 12 months of treatment for Abatacept+MTX vs. Placebo+MTX.
	  ○ Adalimumab: 2 Metaanalysen zeigten signifikante besseres Ansprechen bei ACR20/50/70 und DAS28 bei ADA+MTX vs. Placebo+MTX.
	  ○ Anakinra: 1 Meta-Analyse zeigte signifikant bessere Outcomes (ACR20/50/70, HAQ und Patient Global Assessment) für Anakinra+MTX vs. Placebo+MTX.
	  ○ Certolizumab pegol: 1 Meta-Analyse mit 5 RCTs zeigte signifikant bessere Outcomes (ACR50, Remission und Lebensqualität) für Certolizumab+MTX vs. Placebo+MTX.
	  ○ Etanercept: 2 Meta-Analysen zeigten signifikant bessere Outcomes (ACR50 nach 6 Monaten) für Etanercept +MTX vs. Placebo+MTX.
	  ○ Golimumab: 1 Meta-Analyse zeigte signifikant bessere Outcomes (ACR50, Remission, physical function und disease activity) für Golimumab +MTX vs. Placebo+MTX.
	  ○ Infliximab: 4 Meta-Analysen zeigten signifikant bessere Outcomes (u.a. ACR50) für Infliximab+MTX vs. Placebo+MTX.
	  ○ Rituximab: Keine Meta-Analyse, aber vier RCTS, die eine Wirksamkeit von Rituximab+MTX vs. Placebo+MTX hinsichtlich ACR20/50/70 zeigten.
	  ○ Tocilizumab: 2 Meta-Analysen zeigten signifikant bessere Outcomes (ACR50, Remission und Lebensqualität) für Tocilizumab +MTX vs. Placebo+MTX.
	Key Question 2. Adverse events - RA
	Hinsichtlich AEs waren die Erkrankungen gemischt und die überwiegende Evidenz aus nonRCTs. Lediglich ein RCT verglich AEs zwischen Abatacept und Infliximab: Abatacept resulted in lower rates of serious AEs (9.6 vs. 18.2%), serious infections (1.9 vs. 8.5%) and discontinuations due to AEs (3.2 vs. 7.3%).

	4. Fazit der Autoren For rheumatoid arthritis, low-and moderate-strength evidence indicated that some targeted immune modulators are more efficacious than others. Multiple placebo-controlled randomized controlled trials and meta-analyses provided evidence on the general efficacy of abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, and tocilizumab. Most of these studies were conducted in patients who had

	failed synthetic disease-modifying antirheumatic drug treatment. *5. Kommentar zum Review* • *Untersuchte Wirkstoffe nur für mittelschwere bis schwere RA zugelassen, Operationalisierung bei Einschluss unklar* • *Funding: The Drug Effectiveness Review Project, composed of 12 organizations including 11 State Medicaid agencies, and the Canadian Agency for Drugs and Technology in Health commissioned and funded for this report. These organizations selected the topic of the report and had input into its Key Questions. The content and conclusions of the report were entirely determined by the Evidence-based Practice Center researchers. The authors of this report have no financial interest in any company that makes or distributes the products reviewed in this report.*
Chauffier K et al., 2012 [4]. Effect of biotherapies on fatigue in rheumatoid arthritis: a systematic review of the literature and meta-analysis	1. Fragestellung To assess the clinically relevant effect of available biotherapies on fatigue vs placebo in patients with established RA in two clinical situations: • inadequate response to conventional DMARD (IR-DMARD) and • inadequate response to anti-TNF (IR-anti-TNF).
	2. Methodik Population: Adult patients with rheumatoid arthritis. Intervention / Komparator: biotherapy in association with conventional DMARD compared with placebo with conventional DMARD Endpunkt: fatigue (whatever the scale used and the time points) Suchzeitraum: bis Oktober 2010 Anzahl eingeschlossene Studien/Patienten (Gesamt): 10/3 837 Qualitätsbewertung der Studien: Jadad scale Heterogenitätsanalysen: When I2 was considered as too high (I2>50%), a random effect was used for the meta-analysis Publication bias: funnel plot
	3. Ergebnisdarstellung <u>Qualität der Studien:</u> mean Jadad score: 4.1, symmetrical funnel plot shows that there is no publication bias <u>Wirksamkeit hinsichtlich Fatigue</u> **Patienten mit RA und Therapie mit IR-DMARDs oder IR-anti-TNF** *Biotherapies + DMARD vs. placebo + DMARD* The overall ES [effect size] of all biotherapies vs placebo was considered as

	small at 6 months of treatment with an ES = 0.45 (95% CI 0.31, 0.58). *anti-TNFs +DMARD vs placebo +DMARD* The overall ES [effect size] of anti-TNFs vs placebo on fatigue was small: 0.36 (95% CI 0.21, 0.51) **Patienten mit aktiver RA und Therapie mit konventionellen DMARDs** *biotherapies +DMARD vs placebo + DMARD* In patient with IR-DMARD, biotherapies at 6 months had a small impact with an overall ES [effect size] of 0.38 (95% CI 0.30, 0.46). **Patienten mit aktiver RA und Therapie mit IR-anti-TNF** *biotherapies + DMARD vs placebo +DMARD* Overall effect on fatigue was moderate as well: ES [effect size] = 0.57 (95% CI 0.27, 0.86)
	4. Fazit der Autoren: […] this review of the literature and meta-analysis of RCTs suggest a small effect of biotherapies on fatigue in established RA after 6 months of treatment. *5. Kommentar zum Review* • *Untersuchte Wirkstoffe nur für mittelschwere bis schwere RA zugelassen, Operationalisierung bei Einschluss unklar* • *Funding: Abbott France pharmaceutical company provided support by organizing a meta-analysis methods workshop, but played no further role in the project.* • *Disclosure statement: The authors have declared no conflicts of interest.*
Donahue KE et al., 2012 [7]. 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. <u>Key Questions (KQs):</u> 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: o Disease activity o Radiographic joint damage o Remission • KQ 2: o Functional capacity o Quality of life o Patient-reported symptoms • KQ 3: o Harms, tolerability, adherence, adverse effects • KQ 4: o Benefits and harms in subgroups based on stage, history of prior therapy, demographics, concomitant therapies, comorbidities Suchzeitraum: 1980 – 02/2011 Nur RCTs, Beobachtungsstudien mit mehr als 100 Patienten, systematische Reviews Anzahl eingeschlossene Studien/Patienten (Gesamt): o 31 head-to-head RCTs o 1 head-to-head nicht-randomisiert/kontrollierte Studie o 44 Placebo-kontrollierte Studien o 28 Metaanalysen oder systematische Reviews o 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: 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; for quality of observational studies, criteria outlined by Deeks et al., 2003 (graded the strength of evidence for the outcomes determined) used

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.

Direkter Vergleich: Adatacept vs. Infliximab: kein Unterschied nach 1 Jahr1:

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

Key Comparisons	Efficacy Strength of Evidence	Harms Strength of Evidence
Oral DMARD vs. Oral DMARD		

[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.

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)	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	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	No differences in tolerability; more patients stayed on MTX long term. **Low** Mixed results for specific adverse events.
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	Withdrawal rates attributable to adverse events higher with combination. **Low** Insufficient evidence for specific adverse events.

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	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	Discontinuation rates and severe adverse events higher with infliximab. **Low**

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

Key Comparisons	Efficacy Strength of Evidence	Harms Strength of Evidence
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	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
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	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**	No differences in adverse events in efficacy studies. **Low** Insufficient evidence on differences in the risk for rare but severe adverse events. **Insufficient**

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

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	Substantially higher rates of serious adverse events from combination of two biologic DMARDs than from monotherapy. **Moderate**

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

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	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
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

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

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**	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	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	No differences in serious adverse events between groups. **Low**
	4. 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. Kommentar zum Review* • *nicht immer eindeutige Angaben zur Vorbehandlung* • *Die meisten Studien waren von angemessener methodischer Qualität.*		
Orme ME et al., 2012 [20]. Systematic review and network meta-analysis of combination and monotherapy treatments in disease-	1. Fragestellung Wirksamkeit von EU licensed-dose Biologica-Kombinationen bei RA Patienten mit unzureichendem Ansprechen auf ein oder mehrere DMARDs		
	2. Methodik 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		

modifying antirheumatic drug-experienced patients with rheumatoid arthritis	combination with a DMARD or as a monotherapy Komparator (combination analysis) or placebo (monotherapy analysis) Endpunkte: ACR 20/50/70 response rates Suchzeitraum: 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. publication bias: funnel plots with Egger's linear regression test of asymmetry
	3. Ergebnisdarstellung: *Systematic review results* ○ 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 ○ risk of bias considered low for the majority of included studies ○ 5 studies: risk of bias was unclear, due to incomplete reporting ○ 1 study considered to have a high risk of bias, as there was no concealment of treatment allocation (and several other parameters were unclear) *Meta-analysis results for combination-therapy analysis* ○ 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 *Meta-analysis results for monotherapy analysis* ○ Monotherapie mit Etanercept signifikant besser als Sulfasalazin bzgl. ACR 20/50/70
	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. Kommentar zum Review* • *Schweregrad der Erkrankung spielte keine Rolle bei der Auswertung der Primärstudien.* • *This study was sponsored by Pfizer Ltd, UK. Michelle Orme,*

	Katherine MacGilchrist, and Stephen Mitchell were paid consultants to Pfizer Ltd, UK in connection with this study. Dean Spurden and Alex Bird are paid employees of Pfizer Ltd, UK.
Malottki K et al., 2011 [16]. 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: Bis 2009 Anzahl eingeschlossene Studien/Patienten (Gesamt): 5 RCTs, o 1 comparative study o 1 controlled study o 28 uncontrolled studies
	3. Ergebnisdarstellung <u>Quantity and quality of evidence:</u> 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. <u>Comparative effectiveness:</u> 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. *5. Kommentar zum Review* • *Schweregrad der Erkrankung nicht definiert* • *Interessenkonflikte dargelegt* • *vom NICE finanziert*

Singh JA et al., 2016 [29].

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) laboratory monitoring for traditional DMARDs.

Methodik

Grundlage der Leitlinie: klinische Fragestellungen konsentiert, PICO-Systematik angewendet, systematische Literarturrecherche, Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology (available at www.gradeworkinggroup.org), Patientenvertretung involviert, Interessenkonflikte dargelegt

LoE/GoR:

	Strong recommendation	*Conditional recommendation*
Patients	**Most people in your situation would want the recommended course of action and only a small proportion would not**	*The majority of people in your situation would want the recommended course of action, but many would not**
Clinicians	**Most patients should receive the recommended course of action**	*Be prepared to help patients to make a decision that is consistent with their own values*
Policy makers	**The recommendation can be adapted as a policy in most situations**	*There is a need for substantial debate and involvement of stakeholders*

Figure 1. Implications of strong and conditional GRADE (Grading of Recommendations Assessment, Development, and Evaluation) methodology recommendations (154). * = majority means >50% of the people.

Freitext/Empfehlungen/Hinweise

Recommendations for Early RA Patients

- **For patients with moderate or high disease activity despite DMARD therapy (with or without glucocorticoids), we strongly recommend treatment with a combination of DMARDs or a TNFi or a non-TNF biologic, with or without methotrexate (MTX) in no particular order of preference, rather than continuing DMARD monotherapy alone.** Biologic therapy should be used in combination with MTX over biologic monotherapy,

when possible, due to superior efficacy.

PICO A.7. The recommendation is strong despite the low quality of evidence because, for a patient failing DMARD monotherapy, clinical experience and indirect evidence support the benefits of adding these treatment options, and recommending no additional treatment is not an option. When deciding which therapy to use, considerations may include cost, comorbidities, burden of taking medications (i.e., 1 versus multiple, oral versus other routes) and side-effect profile. The panel also voted that biologic therapy should be used in combination with MTX, when possible, due to superior efficacy of this combination over biologic monotherapy.

26. Van Vollenhoven RF, et al. Conventional combination treatment versus biological treatment in methotrexaterefractory early rheumatoid arthritis: 2 year follow-up of the randomised, non-blinded, parallel-group Swefot trial. Lancet 2012;379:1712–20.

27. Kume K, et al. Tocilizumab monotherapy reduces arterial stiffness as effectively as etanercept or adalimumab monotherapy in rheumatoid arthritis: an open-label randomized controlled trial. J Rheumatol 2011;38:2169–71.

28. Weinblatt ME, et al. Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: findings of a phase IIIb, multinational, prospective, randomized study. Arthritis Rheum 2013;65:28–38.

- *If disease activity remains moderate or high despite DMARDs:*
    - *use a TNFi monotherapy over tofacinib monotherapy*
    - *use a TNFi + MTX over tofacinib + MTX*

PICOs A.8 and A.9. The recommendation is conditional because 1) the evidence is low quality, and 2) there are potential longer-term safety concerns related to tofacitinib that need more study, partly related to the shorter experience using tofacitinib.

29. Fleischmann R, et al. Phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) or adalimumab monotherapy versus placebo in patients with active rheumatoid arthritis with an inadequate response to disease-modifying antirheumatic drugs. Arthritis Rheum 2012;64:617–29.

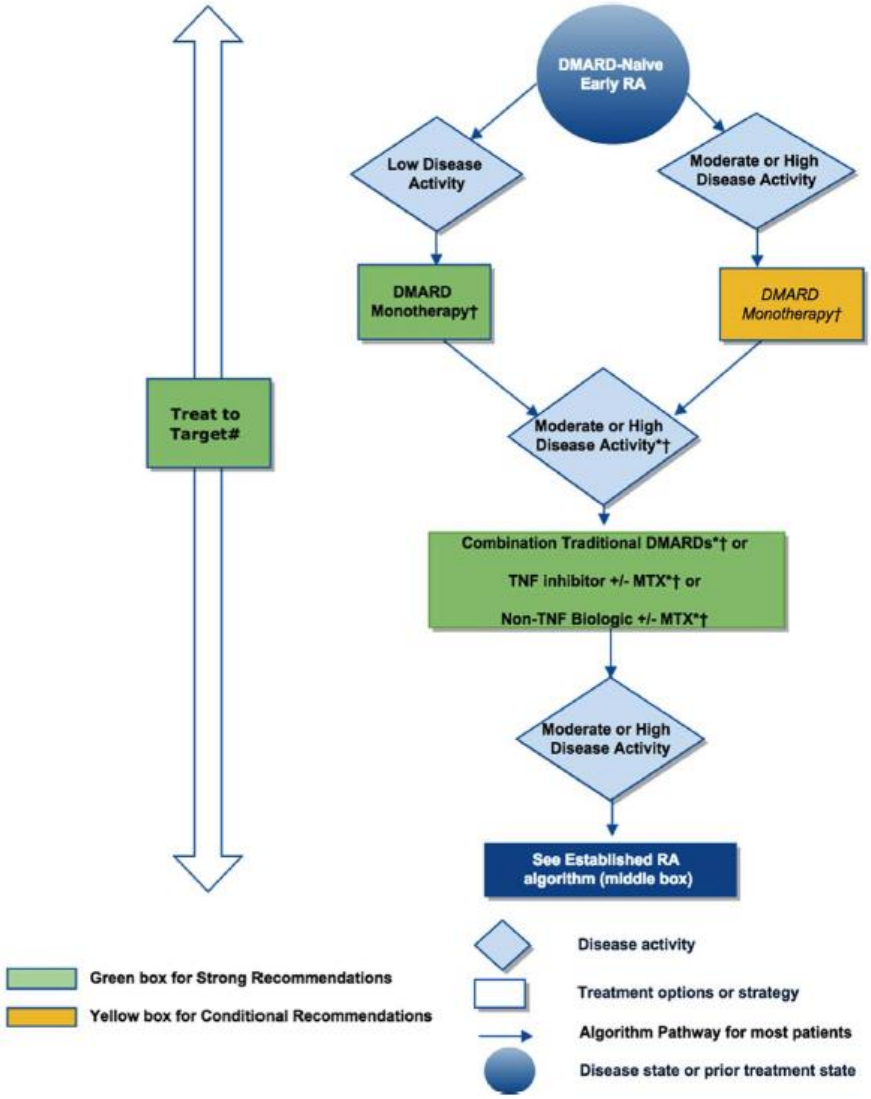
30. Van Vollenhoven RF, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. N Engl J Med 2012;367:508–19.

- *For patients with moderate or high disease activity despite any of the above DMARD or biologic therapies, we conditionally recommend adding low-dose glucocorticoids (defined as ≤10 mg/day of prednisone or equivalent).* Low-dose glucocorticoids may also be used in patients who need a bridge until realizing the benefits of DMARD therapy. The risk/benefit ratio of glucocorticoid therapy is favorable as long as the dose is low and the duration of therapy is short.

PICOs A.6 and A.12. The recommendation is conditional because 1) the evidence is of low quality, and 2) although glucocorticoid therapy is effective as a short-term (i.e., less than 3 months) therapy to "bridge" patients until realizing the benefits of DMARDs, this decision must be balanced by the lack of long-term glucocorticoid safety studies. The risk/benefit ratio of glucocorticoid therapy is favorable as long as the dose is low and the duration of therapy is short.

31. Bakker MF, et al. Low-dose prednisone inclusion in a methotrexatebased, tight control strategy for early rheumatoid arthritis: a randomized trial. Ann InternMed 2012;156:329–39.

	32. Montecucco C, et al. Low-dose oral prednisone improves clinical and ultrasonographic remission rates in early rheumatoid arthritis: results of a 12-month open-label randomised study. Arthritis Res Ther 2012;14:R112. 33. Todoerti M, et al. Early disease control by low-dose prednisone comedication may affect the quality of remission in patients with early rheumatoid arthritis. Ann N Y Acad Sci 2010;1193:139–45. 34. Choy EH, et al. Factorial randomised controlled trial of glucocorticoids and combination disease modifying drugs in early rheumatoid arthritis. Ann Rheum Dis 2008;67:656–63. 35. Svensson B, et al. Low-dose prednisolone in addition to the initial disease-modifying antirheumatic drug in patients with early active rheumatoid arthritis reduces joint destruction and increases the remission rate: a two-year randomized trial. Arthritis Rheum 2005;52:3360–70. 36. Wassenberg S, et al, for the Low-Dose Prednisolone Therapy Study Group. Very low-dose prednisolone in early rheumatoid arthritis retards radiographic progression over two years: a multicenter, double-blind, placebocontrolled trial. Arthritis Rheum 2005;52:3371–80. 37. Capell HA, et al. Lack of radiological and clinical benefit over two years of low-dose prednisolone for rheumatoid arthritis: results of a randomised controlled trial. Ann Rheum Dis 2004;63:797–803. • *For patients experiencing a flare of RA, we conditionally recommend adding short-term glucocorticoids (< 3 months of treatment) at the lowest possible dose for the shortest possible duration, to provide a favorable benefit-risk ratio for the patient.* **PICOs A.10 and A.11.** The recommendation is conditional because the evidence is of low quality because it is indirect, and the risk/benefit ratio of glucocorticoid therapy is favorable as long as the dose is low and duration of therapy is short. 38. Van Everdingen AA, et al. Low-dose prednisone therapy for patients with early active rheumatoid arthritis: clinical efficacy, diseasemodifying properties, and side effects: a randomized, double-blind, placebo-controlled clinical trial. Ann Intern Med 2002;136:1–12. 39. Kirwan JR, et al. A randomised placebo controlled 12 week trial of budesonide and prednisolone in rheumatoid arthritis. Ann Rheum Dis 2004;63:688–95. 40. Durez P, et al. Treatment of early rheumatoid arthritis: a randomized magnetic resonance imaging study comparing the effects of methotrexate alone, methotrexate in combination with infliximab, and methotrexate in combination with intravenous pulse methylprednisolone. Arthritis Rheum 2007;56:3919–27. 41. Choy EH, et al. A two year randomised controlled trial of intramuscular depot steroids in patients with established rheumatoid arthritis who have shown an incomplete response to disease modifying antirheumatic drugs. Ann Rheum Dis 2005;64:1288–93. 42. Gerlag DM, et al. Effects of oral prednisolone on biomarkers in synovial tissue and clinical improvement in rheumatoid arthritis. Arthritis Rheum 2004;50:3783–91. 43. Ciconelli RM, et al. A randomized double-blind controlled trial of sulphasalazine combined with pulses of methylprednisolone or placebo in the treatment of rheumatoid arthritis. Br J Rheumatol 1996;35:150–4.



Recommendations for Established RA Patients

- **For patients with moderate or high disease activity despite DMARD monotherapy including methotrexate, we strongly recommend using combination DMARDs or adding a TNFi or a non-TNF biologic or tofacitinib (all choices with or without methotrexate) in no particular order of preference, rather than continuing DMARD monotherapy alone.** Biologic therapy should be used in combination with MTX over biologic monotherapy, when possible, due to its superior efficacy.

PICO B.5. The recommendation is strong despite moderate to very low quality of evidence because for a patient failing DMARD monotherapy, clinical experience and indirect evidence support the benefits of adding these treatment options, and recommending no treatment is not an option. The panel also voted that biologic therapy should be used in combination with MTX, when possible, due to superior efficacy of this combination over biologic monotherapy.

23. Moreland LW, et al. A randomized comparative effectiveness study of oral triple therapy versus etanercept plus methotrexate in early aggressive rheumatoid arthritis: the Treatment of Early Aggressive Rheumatoid Arthritis Trial. Arthritis Rheum 2012;64:2824–35.

	26. Van Vollenhoven RF, et al. Conventional combination treatment versus biological treatment in methotrexaterefractory early rheumatoid arthritis: 2 year follow-up of the randomised, non-blinded, parallel-group Swefot trial. Lancet 2012;379:1712–20. 29. Fleischmann R, et al. Phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) or adalimumab monotherapy versus placebo in patients with active rheumatoid arthritis with an inadequate response to disease-modifying antirheumatic drugs. Arthritis Rheum 2012;64:617–29. 30. Van Vollenhoven RF, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. N Engl J Med 2012;367:508–19. 47. Ostergaard M, et al. Significant improvement in synovitis, osteitis, and bone erosion following golimumab and methotrexate combination therapy as compared with methotrexate alone: a magnetic resonance imaging study of 318 methotrexate-naive rheumatoid arthritis patients. Arthritis Rheum 2011;63:3712–22. 48. Emery P, et al. Golimumab, a human anti–tumor necrosis factor a monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naive patients with active rheumatoid arthritis: twenty-four–week results of a phase III, multicenter, randomized, double-blind, placebocontrolled study of golimumab before methotrexate as firstline therapy for early-onset rheumatoid arthritis. Arthritis Rheum 2009;60:2272–83. 50. Gabay C, et al. Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. Lancet 2013;381:1541–50. 51. Schiff M, et al. Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: two-year efficacy and safety findings from AMPLE trial. Ann Rheum Dis 2014;73:86–94. 52. Schiff M, 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 rheumatoid arthritis and an inadequate response to methotrexate. Ann Rheum Dis 2008;67:1096–103. 53. Burmester GR, et al. Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomised phase 3 trial. Lancet 2013;381:451–60. 54. Kremer J, et al. Tofacitinib in combination with nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis: a randomized trial. Ann Intern Med 2013;159:253–61. 55. Van der Heijde D, et al. Tofacitinib (CP-690,550) in patients with rheumatoid arthritis receiving methotrexate: twelvemonth data from a twenty-four–month phase III randomized radiographic study. Arthritis Rheum 2013;65:559–70. 56. Fleischmann R, et al. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. N Engl J Med 2012; 367:495–507. 57. Kremer JM, et al. A phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) versus placebo in combination with background methotrexate in patients with active rheumatoid arthritis and an inadequate response to methotrexate alone. Arthritis Rheum 2012;64:970–81. 58. Tanaka Y, et al, and the Tofacitinib Study Investigators. Phase II study of tofacitinib (CP-690,550) combined with methotrexate in patients with rheumatoid arthritis and an inadequate response to methotrexate. Arthritis Care Res (Hoboken) 2011;63:1150–8. 59. O'Dell JR, et al. Therapies for active rheumatoid arthritis after methotrexate failure. N Engl J Med 2013;369:307–18. <u>For all scenarios for established RA below, treatment may be with or without MTX.</u> • **For moderate or high disease activity despite TNFi therapy in patients currently not on a DMARD, we strongly recommend that one or two DMARDs be added to TNFi therapy rather than continuing TNFi therapy alone.** **PICO B.6.** The recommendation is strong because, compared to TNFi monotherapy, TNFi therapy has superior efficacy when used in combination with

	MTX, based on high quality evidence. 60. Kameda H, et al. Etanercept (ETN) with methotrexate (MTX) is better than ETN monotherapy in patients with active rheumatoid arthritis despite MTX therapy: a randomized trial. Mod Rheumatol 2010;20:531–8. 61. Kremer J, et al. Golimumab, a new human anti–tumor necrosis factor a antibody, administered intravenously in patients with active rheumatoid arthritis: forty-eight–week efficacy and safety results of a phase III randomized, double-blind, placebo-controlled study. Arthritis Rheum 2010;62:917–28. 62. Keystone EC, et al. Golimumab, a human antibody to tumour necrosis factor a given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. Ann Rheum Dis 2009;68:789–96. 63. Combe B, et al. Etanercept and sulfasalazine, alone and combined, in patients with active rheumatoid arthritis despite receiving sulfasalazine: a double-blind comparison. Ann Rheum Dis 2006;65:1357–62. 64. Klareskog L, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet 2004;363:675–81. 65. Van Riel PL, et al. Efficacy and safety of combination etanercept and methotrexate versus etanercept alone in patients with rheumatoid arthritis with an inadequate response to methotrexate: the ADORE study. Ann RheumDis 2006;65:1478–83. • *If disease activity is moderate or high despite single TNFi biologic therapy, we conditionally recommend using a non-TNF biologic.* **PICOs B.12 and B.14.** The recommendation is conditional because 1) there is evidence for rituximab's efficacy in patients who have already received TNFi therapy, and for tocilizumab's superiority over a TNFi in patients already receiving MTX/DMARDs, and 2) there is evidence for efficacy of tocilizumab monotherapy. 66. Chatzidionysiou K, van Vollenhoven RF. Rituximab versus anti-TNF in patients who previously failed one TNF inhibitor in an observational cohort. Scand J Rheumatol 2013;42:190–5. 67. Kekow J, Mueller-Ladner U, Schulze-Koops H. Rituximab is more effective than second anti-TNF therapy in rheumatoid arthritis patients and previous TNF a blocker failure. Biologics 2012;6:191–9. 68. Soliman MM, et al, on behalf of the British Society for Rheumatology Biologics Register. Rituximab or a second anti–tumor necrosis factor therapy for rheumatoid arthritis patients who have failed their first anti–tumor necrosis factor therapy? Comparative analysis from the British Society for Rheumatology Biologics Register. Arthritis Care Res (Hoboken) 2012;64:1108–15. 69. Emery P, et al. Rituximab versus an alternative TNF inhibitor in patients with rheumatoid arthritis who failed to respond to a single previous TNF inhibitor: SWITCH-RA, a global, observational, comparative effectiveness study. Ann Rheum Dis 2015;74:979–84. 70. Harrold LR, Reed GW, et al. The comparative effectiveness of abatacept versus anti–tumour necrosis factor switching for rheumatoid arthritis patients previously treated with an anti–tumour necrosis factor. Ann Rheum Dis 2015;74:430–6. 71. Wakabayashi H, et al. Which subgroup of rheumatoid arthritis patients benefits from switching to tocilizumab versus etanercept after previous infliximab failure? A retrospective study. Mod Rheumatol 2012;22:116–21. 72. Finckh A, et al. on behalf of the physicians of the Swiss Clinical Quality Management Program for Rheumatoid Arthritis. B cell depletion may be more effective than switching to an alternative anti–tumor necrosis factor agent in rheumatoid arthritis patients with inadequate response to anti–tumor necrosis factor agents. Arthritis Rheum 2007;56:1417–23. **PICOs B.13 and B.15.** The recommendation is conditional because 1) the evidence is of very low quality, and 2) there is not enough difference in efficacy between non-TNF biologics and tofacitinib to outweigh the long-term safety data and the amount of experience associated with non-TNF biologics. no studies were available, leading to very low quality evidence, and the recommendation was based on clinical experience

- *For patients with moderate or high disease activity despite prior treatment with at least one TNFi and at least one non-TNF-biologic (sequentially, not combined), we conditionally recommend first treating with another non-TNF biologic. However, when a non-TNF biologic is not an option (e.g., patient declines non-TNF biologic therapy due to inefficacy or side effects), we conditionally recommend treatment with tofacitinib.*

PICOs B.16 and B.17. The recommendation is conditional because 1) the evidence is of very low quality, 2) non-TNF biologics have longer-term safety data compared to tofacitinib, 3) there is greater long-term clinical experience with non-TNF biologics compared to tofacitinib, 4) there is not enough difference in efficacy between non-TNF biologics and tofacitinib to outweigh the longer-term safety data and greater amount of experience with non-TNF biologics, and 5) the fact that other non-TNF biologics with different mechanisms of action may be efficacious and worth trying.

no studies were available, leading to very low quality evidence, and the recommendation was based on clinical experience

- *If disease activity is moderate or high despite the use of multiple (2+) TNFi therapies (in sequence, not concurrently), we conditionally recommend non-TNF biologic therapy and then conditionally treating with tofacitinib when a non-TNF biologic is not an option.*

PICOs B.8, B.9, B.10, and B.11. The recommendation is conditional because 1) the evidence is of very low quality, and 2) there is limited evidence, especially for the long-term safety data for tofacitinib.

73. Johnston SS, et al. Risk of infections in rheumatoid arthritis patients switching from anti-TNF agents to rituximab, abatacept, or another anti-TNF agent: a retrospective administrative claims analysis. Semin Arthritis Rheum 2013;43:39–47.

74. Gomez-Reino JJ, et al. Comparative effectiveness of switching to alternative tumour necrosis factor (TNF) antagonists versus switching to rituximab in patients with rheumatoid arthritis who failed previous TNF antagonists: the MIRAR Study. Ann Rheum Dis 2012;71:1861–4.

75. Finckh A, et al. Which subgroup of patients with rheumatoid arthritis benefits from switching to rituximab versus alternative anti–tumour necrosis factor (TNF) agents after previous failure of an anti-TNF agent? Ann Rheum Dis 2010;69:387–93.

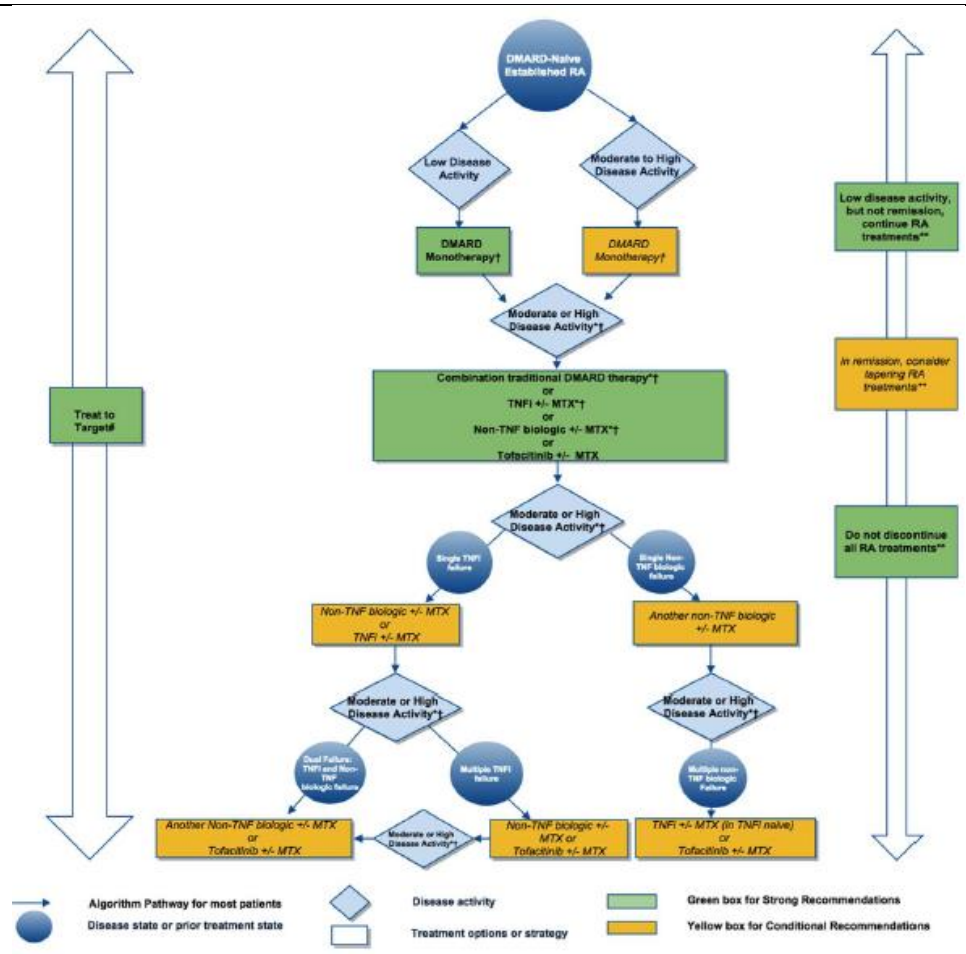
9. *If the disease activity still remains moderate or high despite the use of multiple TNFi therapies, use tofacitinib, with or without MTX, over another TNFi, with or without MTX, if use of a non-TNF biologic is not an option (PICO B.23 and B.24).*	*Low (29,30)*
10. *If disease activity remains moderate 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)*

PICOs B.23 and B.24. The recommendation is conditional because 1) the evidence is of very low quality, 2) improvement in outcomes as measured by the Health Assessment Questionnaire is numerically higher for patients randomized to tofacitinib compared to TNFi in an RCT; however, long-term safety data for tofacitinib are not yet available, and 3) some patients may prefer an oral formulation over an injection.

29. und 30. (siehe oben)

PICOs B.21 and B.22. The recommendation is conditional for the same reasons as cited above for PICOs B.16 and B.17 (except reason #2).

	29. und 30. (siehe oben) **PICOs B.19 and B.20.** The recommendation is conditional for the same reasons as cited above for PICOs B.23 and B.24. 29. (siehe oben) • *If disease activity is moderate or high despite any of the above DMARD or biologic therapies, we conditionally recommend adding low-dose glucocorticoids.* **PICOs B.26 and B.27.** The recommendation is conditional because the risk/benefit ratio of glucocorticoid therapy is favorable as long as the dose is low and duration of therapy is short. 33. Todoerti M, et al. Early disease control by low-dose prednisone comedication may affect the quality of remission in patients with early rheumatoid arthritis. Ann N Y Acad Sci 2010;1193:139–45. 41. Choy EH, et al. A two year randomised controlled trial of intramuscular depot steroids in patients with established rheumatoid arthritis who have shown an incomplete response to disease modifying antirheumatic drugs. Ann Rheum Dis 2005;64:1288–93. 76. Buttgereit F, et al. Low-dose prednisone chronotherapy for rheumatoid arthritis: a randomised clinical trial (CAPRA-2). Ann Rheum Dis 2013;72:204–10. 77. Hansen M, et al. A randomised trial of differentiated prednisolone treatment in active rheumatoid arthritis: clinical benefits and skeletal side effects. Ann Rheum Dis 1999;58:713–8. • *If patients with established RA experience an RA flare while on DMARD, TNFi, or non-TNF biologic therapy, we conditionally recommend adding short-term glucocorticoids (< 3 months of treatment) at the lowest possible dose and for shortest possible duration to provide the best benefit-risk ratio for the patient.* **PICOs B.28 and B.29.** The recommendation is conditional because 1) the evidence is of very low quality, and 2) the risk/benefit ratio of glucocorticoid therapy is favorable as long as the dose is low and duration of therapy is short. 40. bis 43. (siehe oben)

	
National Institute for Health and Care Excellence, 2009 [18]. **last updated 2015** Rheumatoid arthritis in adults: management	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.“ Update information: 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. Sonstige methodische Hinweise: Obwohl die Leitlinie mit Dezember 2015 datiert und damit gültig ist, wurden die Empfehlungen zur medikamentösen Therapie seit 2009 nicht mehr verändert. Dem „review decision report“ ist zu entnehmen, dass eine Aktualisierung notwendig ist. Dazu werden die Ergbenisse der Arbeitsgruppe Stevenson et al. 2016 erwartet (siehe oben). Derzeit läuft der Aktualsierungsprozess für die Leitlinie. Die Vreöffentlichung wird Anfang 2018 erwartet.

	Freitext/Empfehlungen/Hinweise **1.4 Pharmacological management** 1.4.1 DMARDS *Introducing and withdrawing DMARDs* 1.4.1.3 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] 1.4.1.4 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] 1.4.1.5 In people with established RA whose disease is stable, cautiously reduce dosages of disease-modifying or biological drugs. Return promptly to diseasecontrolling dosages at the first sign of a flare. [2009] 1.4.1.6 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] 1.4.1.7 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] 1.4.2 Glucocorticoids 1.4.2.1 Offer short-term treatment with glucocorticoids for managing flares in people with recent-onset or established disease to rapidly decrease inflammation. [2009] 1.4.2.2 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] 1.4.3 Biological drugs Please see our web page on arthritis for other NICE technology appraisal guidance on biological drugs for RA. 1.4.3.1 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[3]. [2009] 1.4.3.2 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[3]. [2009] 1.4.3.3 Do not offer the combination of tumour necrosis factor-α (TNF-α) inhibitor therapy and anakinra for RA. [2009] [2] For example, because of comorbidities or pregnancy, during which certain drugs would be contraindicated. [3] These recommendations are from 'Anakinra for rheumatoid arthritis', NICE technology appraisal guidance 72. The GDG reviewed the evidence on anakinra but made no changes to the recommendations.
Smolen JS et al., 2014 [30]. **European League against Rheumatism (EULAR)** EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheuma	Fragestellung/Zielsetzung: Updating the 2010 EULAR recommendations for the management of RA. Methodik Grundlage der Leitlinie: 4 systematische Übersichtsarbeiten und (teilanonym.) Konsensus-prozesse2, evidenz- und interdisziplinär (Rheumatologie, Patientenvertretung, Gesundheitsökonomie, Infektiologie) konsentierte Leitlinie 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: 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

[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.

tic drugs: 2013 update	consultation and/or speaking engagements ('R'), research funding ('F') or 'none'. • Funding: EULAR
	Freitext/Empfehlungen/Hinweise • 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%)** 87 Leirisalo-Repo M, et al. Infliximab for 6 months added on combination therapy in early rheumatoid arthritis: 2-year results from an investigator-initiated, randomised, double-blind, placebo-controlled study (the NEO-RACo Study). Ann Rheum Dis 2013;72:851–7. 88 O'Dell JR, et al. Therapies for Active Rheumatoid Arthritis after Methotrexate Failure. N Engl J Med 2013;369:307–18. 89 Klarenbeek NB, et al. The impact of four dynamic, goal-steered treatment strategies on the 5-year outcomes of rheumatoid arthritis patients in the BeSt study. Ann Rheum Dis 2011;70:1039–46. 102 Vastesaeger N, et al. A pilot risk model for the prediction of rapid radiographic progression in rheumatoid arthritis. Rheumatology (Oxford) 2009;48:1114–21. 103 Visser K, et al. A matrix risk model for the prediction of rapid radiographic progression in patients with rheumatoid arthritis receiving different dynamic treatment strategies: post hoc analyses from the BeSt study. Ann Rheum Dis 2010;69:1333–7. 104 Moreland LW, et al. Two-year radiographic results from the TEAR trial. Arthritis Rheum 2010;62(Suppl):S568–9. • 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%)** 29 van Vollenhoven RF, et al. Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in patients with early rheumatoid arthritis (Swefot trial): 1-year results of a randomised trial. Lancet 2009;374:459–66. 36 Gabay C, et al. Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. Lancet 2013;381:1541–50. 60 Heimans L, et al. A two-step treatment strategy trial in patients with early arthritis aimed at achieving remission: the IMPROVED study. Ann Rheum Dis 2013. Published Online First: 28 May 2013. doi:10.1136/annrheumdis-2013-203243 63 Burmester G, et al. Efficacy, pharmacokinetics, and safety of different doses of methotrexate in combination with adalimumab: results from the CONCERTO trial. Ann Rheum Dis 2013;72(Suppl 3):72. 88 O'Dell JR, et al. Therapies for Active Rheumatoid Arthritis after Methotrexate Failure. N Engl J Med 2013;369:307–18. 97 Goekoop-Ruiterman YP, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): A randomized, controlled trial. Arthritis Rheum 2005;52:3381–90. 105 Morel J, et al. Prospective follow-up of tocilizumab treatment in 1100 patients with refractory rheumatoid arthritis: tolerance data from the french registry regate (registry–roactemra). Ann Rheum Dis 2013;72 (Suppl 3):456. 106 Hishitani Y, et al. Retention of tocilizumab and anti-tumour necrosis factor drugs in the treatment of rheumatoid arthritis. Scand J Rheumatol 2013;42:253–9. 107 Horak P, et al. Abatacept and its use in the treatment of rheumatoid arthritis (RA) in the Czech Republic-data from the ATTRA registry. Clin Rheumatol 2013;32:1451–8. 108 Gottenberg JE, et al. Risk factors for severe infections in patients with rheumatoid arthritis

treated with rituximab in the autoimmunity and rituximab registry. Arthritis Rheum 2010;62:2625–32.

109 Godot S, et al. Safety of surgery after rituximab therapy in 133 patients with rheumatoid arthritis: Data from the AutoImmunity and Rituximab registry. Arthritis Care Res (Hoboken) 2013. doi:10.1002/acr.22056. [Epub ahead of print 10 Jun 2013].

110 Weinblatt ME, et al. Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: findings of a phase IIIb, multinational, prospective, randomized study. Arthritis Rheum 2013;65:28–38.

111 Tak PP, et al. Inhibition of joint damage and improved clinical outcomes with rituximab plus methotrexate in early active rheumatoid arthritis: the IMAGE trial. Ann Rheum Dis 2011;70:39–46.

112 Emery P, et al. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phase IIB randomized, double-blind, placebo-controlled, dose-ranging trial. Arthritis Rheum 2006;54:1390–400.

113 Buch MH, et al. Updated consensus statement on the use of rituximab in patients with rheumatoid arthritis. Ann Rheum Dis 2011;70:909–20.

114 Strangfeld A, et al. Risk of cancer recurrence or new tumors in RA patients with prior malignancies treated with various biologic agents. Arhritis Rheum 2013; (ACR 2013 Abstract online (https://ww2.rheumatology.org/apps/MyAnnualMeeting/Abstract/36584).

115 Yoo DH, et al. A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study. Ann Rheum Dis 2013;72:1613–20.

116 Park W, et al. A randomised, double-blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study. Ann Rheum Dis 2013;72:1605–12.

117 Krieckaert CL, et al. Methotrexate reduces immunogenicity in adalimumab treated rheumatoid arthritis patients in a dose dependent manner. Ann Rheum Dis 2012;71:1914–5.

118 Jones G, et al. Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study. Ann Rheum Dis 2010;69:88–96.

119 Nishimoto N, et al. Study of active controlled monotherapy used for rheumatoid arthritis, an IL-6 inhibitor (SAMURAI): evidence of clinical and radiographic benefit from an x ray reader-blinded randomised controlled trial of tocilizumab. Ann Rheum Dis 2007;66:1162–7.

120 Burmester GR, et al. Tocilizumab (TCZ) in combination and monotherapy versus methotrexate (MTX) in MTX-naive patients (pts) with early rheumatoid arthritis (RA): clinical and radiographic outcomes from a randomised, placebo-controlled trial. Ann Rheum Dis 2013;72(Suppl):OP041.

121 Bakker MF, et al. Tight control in the treatment of rheumatoid arthritis: efficacy and feasibility. Ann Rheum Dis 2007;66(Suppl 3):iii56–60.

122 Dougados M, et al. Adding tocilizumab or switching to tocilizumab monotherapy in methotrexate inadequate responders: 24-week symptomatic and structural results of a 2-year randomised controlled strategy trial in rheumatoid arthritis (ACT-RAY). Ann Rheum Dis 2013;72:43–50.

123 Emery P, et al. Combination etanercept and methotrexate provides better disease control in very early (<=4 months) versus early rheumatoid arthritis (>4 months and <2 years): post hoc analyses from the COMET study. Ann Rheum Dis 2012;71:989–92.

124 van Riel PL, et al. Efficacy and safety of combination etanercept and methotrexate versus etanercept alone in patients with rheumatoid arthritis with an inadequate response to methotrexate: the ADORE study. Ann Rheum Dis 2006;65:1478–83.

125 Soubrier M, et al. Evaluation of two strategies (initial methotrexate monotherapy vs its combination with adalimumab) in management of early active rheumatoid arthritis: data from the GUEPARD trial. Rheumatology (Oxford) 2009;48:1429–34.

126 Fleischmann R, et al. Long-Term Outcomes of Early Rheumatoid Arthritis Patients Initiated with Adalimumab Plus Methotrexate Compared with Methotrexate Alone Following a Targeted Treatment Approach. Arthritis Rheum 2012;64(Suppl):S335–6.

127 Smolen JS, et al. Treating Rheumatoid Arthritis to Target: Outcomes and Predictors in Early Rheumatoid Arthritis Patients Treated with Adalimumab Plus Methotrexate, Methotrexate Alone, or Methotrexate Plus Subsequent Adalimumab. Arthritis Rheum 2011;63(Suppl):S665. Ref Type:

	Abstract. 128 Kavanaugh A, et al. Withrawal of adalimumab in early rheumatoid arthritis patients who attained stable low disease activity with adalimumab plus methotrexate: esults of a phase 4, double-blind, placebo-controlled trial. Rheumatology (Oxford) 2012;51(Suppl 3):iii27. 129 Detert J, et al. Induction therapy with adalimumab plus methotrexate for 24 weeks followed by methotrexate monotherapy up to week 48 versus methotrexate therapy alone for DMARD-naive patients with early rheumatoid arthritis: HIT HARD, an investigator-initiated study. Ann Rheum Dis 2013;72:844–50. 130 Emery P, et al. Assessing maintenance of remission with reduced dose etanercept plus methotrexate, methotrexate alone, or placebo in patients with early rheumatoid arthritis who achieved remission with etanercept and methotrextate: the PRIZE study. Ann Rheum Dis 2013;72(Suppl 3):399. • 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%)** 131 Huizinga T, et al. Sarilumab for the treatment of moderate-to-severe rheumatoid arthritis: results of a phase 2, randomized, double-blind, placebo-controlled, international study. Ann Rheum Dis 2012;71 (Suppl 3):60. Ref Type: Abstract. 132 Hsu B, et al. Results from a 2-part, proof-of-concept, dose-ranging, randomized, double-blind, placebo-controlled, phase 2 study of sirukumab, a human anti-interleukin-6 monoclonal antibody, in active rheumatoid arthritis patients despite methotrexate therapy. Arthritis Rheum 2011;63(Suppl): S1034. Ref Type: Journal (Full). 133 Mease P, et al. A phase II, double-blind, randomised, placebo-controlled study of BMS945429 (ALD518) in patients with rheumatoid arthritis with an inadequate response to methotrexate. Ann Rheum Dis 2012;71:1183–9. • Tofacitinib may be considered after biological treatment has failed. **(LoE 1b*, GoR A*, SoR 7.6±1.8, 90%)** ***The general statement is evidence based.** 2 Smolen JS, et al. Proposal for a new nomenclature of disease-modifying antirheumatic drugs. Ann Rheum Dis 2014;73:3–5. 8 Schoels M, et al. Economic aspects of treatment options in rheumatoid arthritis: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis 2010;69:995–1003. 13 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. 31 Dorner T, et al. The role of biosimilars in the treatment of rheumatic diseases. Ann Rheum Dis 2013;72:322–8. 134 van Vollenhoven RF, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. N Engl J Med 2012;367:508–19. 135 Burmester GR, et al. Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomised phase 3 trial. Lancet 2013;381:451–60. 136 Fleischmann R, et al. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. N Engl J Med 2012;367:495–507. 137 van der Heijde D, et al. Tofacitinib (CP-690,550) in patients with rheumatoid arthritis on methotrexate: 12-Month data from a 24-month Phase 3 randomized radiographic study. Arthritis Rheum 2013;65:559–70. 138 Lee EB, et al. Radiographic, Clinical and Functional Comparison of Tofacitinib Monotherapy Versus Methotrexate in Methotrexate-Nave Patients with Rheumatoid Arthritis. Arthritis Rheum 2012;64(Suppl):S1049. 139 Winthrop KL, et al. Association between the initiation of anti-tumor necrosis factor therapy and

	the risk of herpes zoster. JAMA 2013;309:887–95. 140 Guyatt GH, et al. Incorporating considerations of resources use into grading recommendations. BMJ 2008;336:1170–3. 141 Garber K. Pfizer's first-in-class JAK inhibitor pricey for rheumatoid arthritis market. Nat Biotechnol 2013;31:3–4. 142 Xeljanz Filmtbl 5mg (iH 08/13). 2013. http://www.kompendium.ch/prod/pnr/1234138/de. 143 European Medicines Agency-CHMP. Summary of Opinion (Infliximab biosimilar). 2013. http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/002576/WC500144832.pdf,editors. Ref Type: Online Source. 144 European Medicines Agency. European Medicines Agency recommends approval of first two monoclonal antibody biosimilars. 2013. http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2013/06/WC500144941.pdf. Ref Type: Online Source. 145 European Medical Agency. Xeljanz. 2013. http://www.ema.europa.eu/ema/indexjsp?curl=pages/medicines/human/medicines/002542/smops/Negative/human_smop_000501jsp&mid=WC0b01ac058001d127 (accessed 25 May, 2014). 146 Committee for Medicinal Products for Human Use (CHMP). Meeting highlights from the Committee for Medicinal Products for Human Use (CHMP). 22–25 July 2013. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/07/news_detail_001851.jsp&mid=WC0b01ac058004d5c1. 147 Pfizer. Pfizer Receives CHMP Negative Opinion Regarding Marketing Authorization In Europe For Rheumatoid Arthritis Treatment XELJANZ (tofacitinib citrate). 2013. http://press.pfizer.com/press-release/pfizer-receives-chmp-negative-opinionregarding-marketing-authorization-europe-rheumat (accessed 25 May 2013). * 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 [1]. **Canadian Rheumatology**	Fragestellung/Zielsetzung: <u>Treatment with glucocorticoids</u> • What is the role of glucocorticoids in the management of RA? <u>Treatment with traditional DMARD</u> • When should combination therapy with traditional DMARD be used?

Association (CRA) Recommendations for Pharmacological Management of Rheumatoid Arthritis with Traditional and Biologic Disease-modifying Antirheumatic Drugs	• 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? • 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 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, evidenz- und konsensbasierte Leitlinie 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.*

	Fragestellung/Zielsetzung: Treatment with glucocorticoids • Glucocorticoids (oral, intramuscular, or intraarticular) can be added to DMARD therapy as part of the initial treatment strategy of patients with RA (I), and may be an option for managing flares, as bridge therapy while waiting for DMARD to take effect, or for symptom control if no other options exist (IV). Glucocorticoids should be used in the lowest possible dose and tapered as rapidly as clinically feasible (IV). **(Level I, IV; Strenght A/D)** 20. Cardiel MH. First Latin American position paper on the pharmacological treatment of rheumatoid arthritis. Rheumatology 2006;45 Suppl 2:ii7-ii22. 22. Luqmani R, et al. British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of rheumatoid arthritis (the first two years). Rheumatology 2006;45:1167-9. 23. National Institute for Clinical Excellence (NICE). Rheumatoid arthritis: The management of rheumatoid arthritis in adults: NICE clinical guidance 79; 2009. [Internet. Accessed July 14, 2011.] Available from: http://www.nice.org.uk/nicemedia/pdf/CG79NICEGuideline.pdf 26. Smolen JS, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis 2010;69:964-75. 29. Wolfe F, et al. Consensus recommendations for the assessment and treatment of rheumatoid arthritis. J Rheumatol 2001;28:1423-30. 32. Scottish Intercollegiate Guidelines Network (SIGN). Management of early rheumatoid arthritis: SIGN Publication No. 48 2000; [Internet. Accessed July 14, 2011.] Available from: http://www.sign.ac.uk/guidelines/fulltext/48/index.html 34. Kalla AA, et al. Rheumatoid arthritis: Clinical guideline 2003. South African Med J 2003;93:991-1011. 54. Spanish Society of Rheumatology. Update of the clinical practice guideline for the management of rheumatoid arthritis in Spain; 2007. [Internet. Accessed July 14, 2011.] Available from: http://www.ser.es/ArchivosDESCARGABLES/Proyectos/GUIPCAR_2007/GUIPCAR2007-ENG.pdf 55. 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;69:1010-4. 56. Hoes JN, et al. EULAR evidence-based recommendations on the management of systemic glucocorticoid therapy in rheumatic diseases. Ann Rheum Dis 2007;66:1560-7. *Evidence to recommendation.* The panel agreed with the body of evidence supporting short-term use of GC in the initial management of patients with RA and acknowledged the anecdotal evidence regarding efficacy of GC for managing flares and as bridge therapy. The panel was concerned with the potential for toxicity associated with use of GC, and while they agreed GC should be used in low doses and tapered rapidly, an optimal tapering strategy could not be recommended. When choosing a route of administration, intramuscular or intraarticular steroids allow more control over the total cumulative dose and may be preferred in certain situations. Intraarticular steroids were agreed to be particularly useful for controlling residual synovitis if a few swollen joints remain, as they avoid systemic toxicity. Treatment with MTX/DMARD • 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)

23. siehe oben

29. siehe oben

33. Combe B, et al. EULAR recommendations for the management of early arthritis: Report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2007;66:34-45.

36. Saag KG, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. Arthritis Care Res 2008;59:762-84.

58. Maddison P, et al. Leflunomide in rheumatoid arthritis: Recommendations through a process of consensus. Rheumatology 2005;44:280-6.

66. GPAC: Guidelines and Protocols Advisory Committee. Rheumatoid arthritis: diagnosis and management; 2006. [Internet. Accessed July 14, 2011.] Available from: http://www.bcguidelines.ca/gpac/

68. Katchamart W, et al. Efficacy and toxicity of methotrexate (MTX) monotherapy versus MTX combination therapy with non-biological disease-modifying antirheumatic drugs in rheumatoid arthritis: a systematic review and meta-analysis. Ann Rheum Dis 2009;68:1105-12.

Evidence to recommendation. After reviewing the evidence, the panel agreed that there was sufficient evidence to support the use of MTX as the anchor drug when using combination therapy, although other DMARD combinations may also be considered. Several different combination therapies have been shown to be effective in the treatment of RA, but direct comparative effectiveness data of the different combinations are lacking. The panel therefore agreed it was appropriate to provide a list of combinations supported by evidence and the choice of combination should be left to the discretion of the rheumatologist as a shared decision with the patient, based on individual patient circumstances.

- 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)

2. Haraoui B. Canadian Rheumatology Association position on the use of biologic agents for the treatment of rheumatoid arthritis; 2002. [Internet. Accessed July 14, 2011.] Available from: http://www.rheum.ca/en/ContentPage.asp?sid=81

31. Misra R, et al. Indian Rheumatology Association consensus statement on the management of adults with rheumatoid arthritis. Indian J Rheumatol 2008;3 Suppl:S1-S16.

36. siehe oben

62. Visser K, et al. Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative. Ann Rheum Dis 2009;68:1086-93.

69. Kremer JM, et al. Concomitant leflunomide therapy in patients with active rheumatoid arthritis despite stable doses of methotrexate. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 2002;137:726-33.

70. FDA. FDA Drug Safety Communication: New boxed warning for severe liver injury with arthritis drug Arava (leflunomide); 2010. [Internet. Accessed July 14, 2011.] Available from: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm218679.htm

Evidence to recommendation. The panel recognized that there is evidence from

	RCT supporting the efficacy of MTX + LEF in patients with high disease activity with an inadequate response to MTX and that many patients have been successfully treated with this combination without serious adverse events. The panel considered, however, that in general, other combination therapies of proven efficacy would be preferred over LEF + MTX due to increased GI and hepatotoxicity. The panel also recognized that LEF combination therapy is typically considered after an inadequate response to MTX, and that in this situation it is not desirable to withdraw MTX to treat with LEF as this may result in worsening of disease control. If LEF + MTX is used, liver enzymes should be monitored monthly and dose reduction of LEF (to 10 mg), or MTX should be considered. Similarly, clinicians should exercise caution when combining LEF with other drugs that have the potential to cause liver injury. <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) 2. 20. 26. 29. 31. 34. siehe oben 19. Australian Rheumatology Association (ARA). Updated recommendations for the use of biological agents for the treatment of rheumatic diseases; 2010. [Internet. Accessed Aug 25, 2011.] Available from: http://www.rheumatology.org.au/otherpages/biological-guidelines.asp 27. Spanish Society of Rheumatology. Update of the consensus statement of the Spanish Society of Rheumatology on the management of biologic therapies in rheumatoid arthritis. Reumatol Clin 2010;6:23-36. 35. National Institute for Clinical Excellence (NICE). Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis: NICE technology appraisal guidance 130 (includes a review of technology appraisal guidance 36); 2007. [Internet. Accessed July 14, 2011.] Available from: http://www.nice.org.uk/TA130 39. Fautrel B, et al. Recommendations of the French Society for Rheumatology regarding TNF alpha antagonist therapy in patients with rheumatoid arthritis. Joint Bone Spine 2007;74:627-37. 40. Deighton C, et al. BSR and BHPR rheumatoid arthritis guidelines on eligibility criteria for the first biological therapy. Rheumatology 2010;49:1197-99.51 71. Emery P, et al. WHO collaborating centre consensus meeting on anti-cytokine therapy in rheumatoid arthritis. Rheumatology 2001;40:699-702. 72. Koike R, et al. Japan College of Rheumatology 2009 guidelines for the use of tocilizumab, a humanized anti-interleukin-6 receptor monoclonal antibody, in rheumatoid arthritis. Mod Rheumatol 2009;19:351-7. 73. Ledingham J, Deighton C. Update on the British Society for Rheumatology guidelines for prescribing TNF alpha blockers in adults with rheumatoid arthritis (update of previous guidelines of April 2001). Rheumatology 2005;44:157-63. 74. Mok CC. Consensus on the use and monitoring of anti-TNF-alpha therapies for rheumatic diseases in Hong Kong 2005. APLAR J Rheumatol 2006;9:175-80. 75. Royal College of Nursing (RCN). Assessing, managing and monitoring biologic therapies for inflammatory arthritis: guidance for rheumatology practitioners. Musculoskeletal Care 2003;1:135-40. *Evidence to recommendation.* The present recommendation was developed based on expert opinion taking into account the Canadian practice setting. Biologics, while proven effective in DMARD inadequate responders (DMARD-IR)

	and DMARD-naive patients (see Recommendations 19, 20, 22), are associated with higher costs and potential risks for toxicity. Prior treatment with 2 DMARD in mono or combination therapy was chosen to balance the potential opportunity for a response to DMARD therapy with early initiation of a biologic that may be necessary to reach the treatment target. Three months at target dose was agreed to be a sufficient period to observe a therapeutic effect for most DMARD while minimizing delays in treatment adjustment. • 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) 1. Canadian Agency for Drugs and Technology in Health. Clinical and economic overview: Biological response modifier agents for adults with rheumatoid arthritis; 2010. [Internet. Accessed July 14, 2011.] Available from: www.cadth.ca/media/pdf/TR_RA_Clinical_and_Economic_Overview_e.pdf 2. 19. 22. 26. 31. 35. 36. 39. 73. 74. 75. siehe oben 77. Furst DE, et al. Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2009. Ann Rheum Dis 2010;69 Suppl 1:i2-29. 78. 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. *Evidence to recommendation.* The panel agreed that there was strong evidence to recommend coprescription of MTX with biologic agents. In cases where MTX cannot be used, another DMARD is recommended. If coprescription with MTX or another DMARD is not possible, certain biologic agents may be used in monotherapy. Currently, ETN, ADA, CTZ, ABAT, and tocilizumab are licensed for use as monotherapy in Canada. Patients that have remained in a low disease state taking biologic monotherapy may not need the reintroduction of a DMARD. • 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) 1. 2. 20. 26. 27. 29. 31. 34. 35. 36. 39. 40. 71. 74. 75. 77. siehe oben 21. Kiely PD, et al. Contemporary treatment principles for early rheumatoid arthritis: A consensus statement. Rheumatology 2009;48:765-72. 51. Massardo L, et al. Management of patients with rheumatoid arthritis in Latin America: a consensus position paper from Pan-American League of Associations of Rheumatology and Grupo Latino Americano De Estudio De Artritis Reumatoide. J Clin Rheumatol 2009;15:203-10. 79. Smolen JS, et al. Consensus statement on the initiation and continuation of tumour necrosis factor blocking therapies in rheumatoid arthritis. Ann Rheum Dis 2000;59:504-5. *Evidence to recommendation.* The panel agreed that there was strong evidence that anti-TNF therapy is effective after failure of a DMARD or in patients who are MTX (or DMARD) naive. However, the panel also acknowledged that many patients respond well to initial DMARD therapy and considered the implications of using anti-TNF therapy in DMARD-naïve patients, including added costs and potential risks. Therefore, the panel agreed that in most circumstances anti-TNF therapy should be used after a DMARD-IR. Anti-TNF therapy was acknowledged

as an option in DMARD-naive patients or after failure of DMARD monotherapy in rare situations outlined in the recommendation, consistent with eligibility criteria for biologic trials in MTX-naive patients.

- 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)

1. 19. 26. 27. 36. 77. siehe oben

78. 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.

80. National Institute for Clinical Excellence (NICE). Abatacept for the treatment of rheumatoid arthritis: NICE technology appraisal guidance 141; 2008. [Internet. Accessed July 14, 2011.] Available from: http://www.nice.org.uk/nicemedia/pdf/TA141guidance.pdf

Evidence to recommendation. The panel concluded that there was strong evidence that ABAT is effective after failure of DMARD or anti-TNF therapy. The panel also considered that there is evidence for the efficacy of ABAT in DMARD-naïve patients, but agreed that, in the rare situations where a biologic is being considered as first-line therapy, an anti-TNF would be used.

- 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)

1. 19. 26. 27. 31. 36. 51. 77. 78. siehe oben

43. Soriano ER, et al. Use of rituximab for the treatment of rheumatoid arthritis: The Latin American context. Rheumatology 2008;47:1097-9.

81. National Institute for Clinical Excellence (NICE). Rituximab for the treatment of rheumatoid arthritis: NICE technology appraisal guidance 126; 2007. [Internet. Accessed July 14, 2011.] Available from: http://www.nice.org.uk/nicemedia/pdf/TA126guidance.pdf

82. Smolen JS, et al. Consensus statement on the use of rituximab in patients with rheumatoid arthritis. Ann Rheum Dis 2007;66:143-50.

Evidence to recommendation. The panel agreed that there was strong evidence that RTX is effective after failure of DMARD or anti-TNF therapy in RF-positive patients. The panel also agreed that in certain situations, including patients with a previous history of B cell lymphoma, LTBI, multiple sclerosis, and concomitant vasculitis or overlap syndromes, RTX may be preferred.

- Tocilizumab is recommended for the treatment of patients with RA after an inadequate response to DMARD or anti-TNF therapy. **(Level I; Strength A)**

19. 26. 72. 77. 78. siehe oben

24. Pham T, et al. Tocilizumab: therapy and safety management. Joint Bone Spine 2010;77 Suppl 1:S3-100.

84. National Institute for Clinical Excellence (NICE). Tocilizumab for the treatment of rheumatoid arthritis; 2010. [Internet. Accessed July 14, 2011.] Available from: http://www.nice.org.uk/nicemedia/live/13100/50391/50391.pdf

Evidence to recommendation. The panel agreed that there was strong evidence that TCZ is effective after failure of DMARD or anti-TNF therapy.

- 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)

1. 19. 26. 27. 39. 78. siehe oben

85. National Institute for Health and Clinical Excellence. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor: a systematic review and economic evaluation; 2009 [Internet. Accessed July 14, 2011]. Available from: http://www.nice.org.uk/nicemedia/pdf/RheumatoidArthritisAssessmentReport.pdf

Evidence to recommendation. The panel agreed that there is sufficient evidence to support the role of a second anti-TNF agent or switching to a biologic with a different mechanism of action in patients who fail to respond to the first anti-TNF. As biologic therapy is generally more effective when given in combination with DMARD, adding MTX (or other DMARD if MTX is contraindicated) to biologic monotherapy could also be considered. However, the panel realizes that this situation should be rare, as DMARD coprescription is recommended for all biologic therapy (see Recommendation 15).

Dose/interval adjustment of IFX may be an option; however, evidence is inconclusive. A preference for a particular therapeutic strategy could not be established due to lack of head-tohead trials, therefore the choice should be a shared decision between patient and physician.

- 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

27. 39. 85. siehe oben

86. Cohen SB, et al. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum 2006;54:2793-806.

87. Genovese MC, et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. N Engl J Med 2005;353:1114-23.

88. Emery P, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. Ann Rheum Dis 2008;67:1516-23.

89. Smolen JS, et al. Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor alpha inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. Lancet 2009;374:210-21.

Evidence to recommendation. The panel recognized that there was no direct evidence comparing different therapeutic strategies in patients failing ≥ 2 anti-TNF. Based on the limited evidence extrapolated from RCT and observational studies, the panel agreed that switching to a different mechanism of action is currently the preferred therapeutic strategy for patients with ≥ 2 prior TNF failures.

- 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,

<table>
<tr><td></td><td>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

26. siehe oben

Evidence to recommendation. In view of the lack of evidence evaluating efficacy of biologic or nonbiologic DMARD in patients with an inadequate response to ABAT, RTX, or TCZ, the panel considered possible strategies with potential benefits including switching the treatment to an agent with a different mechanism of action or to a nonbiologic DMARD, if not previously used. Offering enrollment into a clinical trial is also an option in patients who fail to respond to available therapies, although clinical trials, where appropriate, are an option at any time during the treatment of patients with RA. Lastly, as in any other failure scenario, alternative reasons for failure such as patient nonadherence to treatment (either partial or complete) and alternative diagnoses contributing to patients' symptoms (e.g., fibromyalgia) should also be explored with the patient and considered when deciding on the appropriate therapeutic strategy.</td></tr>
<tr><td rowspan="2">Scottish Intercollegiate Guidelines Network, 2011 [25].

Management of early rheumatoid arthritis</td><td>Fragestellung/Zielsetzung:

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.</td></tr>
<tr><td>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:

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

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

Freitext/Empfehlungen/Hinweise

2.1 PRINCIPLES OF MANAGEMENT

Patients with moderate to severe disease activity should:

- be assessed for disease activity using a standardised scoring system such as DAS/DAS28
- be reviewed monthly until remission or a low disease activity score is achieved
- receive treatment with DMARDs, adjusted with the aim of achieving remission or a low DAS/DAS28 score. **(GoR: B)**

43. Grigor C, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the ticora study): A single-blind randomised controlled trial. Lancet 2004;364(9430):263-9. **(LoE 1++)**

2.2 DISEASE MODIFYING ANTI-RHEUMATIC DRUGS

Methotrexate and sulfasalazine are the DMARDs of choice due to their more favorable efficacy and toxicity profiles. **(GoR: A)**

- The efficacy of MTX, intramuscular gold, LEF, penicillamine and SASP, is similar.[64] HCQ is less effective.[65] Intramuscular gold has the highest toxicity and therefore increased treatment drop-out rates compared to SASP, HCQ and MTX.[66] **(LoE 1+ und 1++)**

64. Felson DT, et al. The comparative efficacy and toxicity of second-line drugs in rheumatoid arthritis. Results of two metaanalyses. Arthritis Rheum 1990;33(10):1449-61.

65. Fries JF. ARAMIS and toxicity measurement (Arthritis Rheumatism and Aging Medical Information System). J Rheumatol 1995;22(5):995-7.

66. Maetzel A, et al. Meta-analysis of treatment termination rates among rheumatoid arthritis patients receiving disease modifying anti-rheumatic drugs. Rheumatology (Oxford) 2000;39(9):975-81.

- A systematic review found leflunomide (LEF), methotrexate (MTX) and sulfasalazine (SASP) to have comparable efficacy.[56] MTX has the most favourable efficacy/toxicity trade-off. **(LoE: 1++)**

56. Donahue KE, et al. Systematic review: Comparative effectiveness and harms of disease-

	modifying medications for rheumatoid arthritis. Ann Intern Med 2008;148(2):124-34. 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.[56] Most combinations use MTX as an anchor drug. **(LoE 1++)** <u>Biologics (Empfehlungen nicht als solche hervorgehoben)</u> • 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**.** 72. Kuriya B, et al. Efficacy of initial methotrexate monotherapy versus combination therapy with a biological agent in early rheumatoid arthiritis: a meta-analysis of clinical and radiographic remission. Ann Rheum Dis 2010;69(7):1298-304. **(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] 73. Van Vollenhoven R, et al. Addition of infliximab compared with addition of sulfasalazine and hydroxycholoroquine to methotrexate in patients with early rheumatoid arthritis (Swefot trial): 1-year results of a randomised trial. Lancet 2009;374(9688):459-66. **(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 74. National Institute for Health and Clinical Excellence. Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis. London: NICE; 2007. (NICE technology appraisal guidance 130). Available from url: http://www.nice.org.uk/nicemedia/live/11867/37914/37914.pdf **(LoE 1++)**
Guipcar Group, 2011 [8]. **Spanish Society of Rheumatology (SER)** Update of the CLINICAL	Fragestellung/Zielsetzung: Update of the 2007 GUIPCAR guidelines
	Methodik Grundlage der Leitlinie: Systematische Übersichtsarbeiten und Konsensusprozess, evidenz- und interdisziplinär (Rheumatologie, primary care physician, a nurse, and two physical therapists) konsentierte Leitlinie Suchzeitraum: Update bis Juli 2010 Weitere Kriterien für die Qualität einer Leitlinie: Quellen im jeweiligen Hintergrundtext zu den Empfehlungen zitiert.

PRACTICE GUIDELINE FOR THE MANAGEMENT OF RHEUMATOID ARTHRITIS IN SPAIN	LoE/GoR: LoE: Oxford Centre for Evidence-Based Medicine (March 2011) GoR: A – Based on the results of consistent level 1 studies B – Based on the results of consistent level 2 or 3 studies **or** on extrapolations* from level 1 studies C – Based on the results of level 4 studies **or** on extrapolations* from level 2 or 3 studies D – Based on the results of level 5 studies **or** on troublingly inconsistent or inconclusive studies of any level * "Extrapolations" are where data is used in a situation which has potentially clinically important differences than the original study situation. Sonstige methodische Hinweise: • Competing interests: online einsehbar für alle Autoren • Funding: provided from Pfizer for translating the document into English
	Freitext/Empfehlungen/Hinweise **Changes in treatment** • If response to MTX is unsatisfactory after reaching the maximum dosage and assuring the bioavailability of the agent, the panel recommends the use of LEF or SSZ or an anti-TNF agent as the second step in the treatment ladder, either replacing or in addition to MTX. If MTX toxicity is such as to oblige its withdrawal, the panel recommends using LEF or SSZ or an anti-TNF agent as the second step on the treatment ladder. **[5, D]** • In patients for whom the previously described guidelines are not useful due to lack of efficacy, toxicity or other reasons, use of any of the DMARDs, combinations or other biologic agents is recommended; if these fail, experimental treatments should be tried. **[5, D]** **Treatment with glucocorticoids** • In RA of long duration, the use of low-dose oral glucocorticoids is recommended as anti-inflammatory therapy for symptom control while waiting for the DMARDs to take effect. **[5, D]** **Treatment with non-steroidal anti-inflammatories (NSAIDs)** • The NSAIDs are used to modify the symptoms of RA. The use of NSAIDs is recommended at disease onset, when a new DMARD is introduced, and occasionally when uncontrolled isolated symptoms persist despite good response to a DMARD. **[5, D].** • The need for continuous use of NSAIDs in a patient with RA should be interpreted as inadequate control of inflammatory activity and should, therefore, lead to reassessment of the DMARD regimen. **[5, D]** • All NSAIDs should be used at the full dose for at least 1 week before considering the treatment to have failed. Once symptoms have been controlled, the minimum effective dose should be used. **[5, D]** • There is no evidence that some NSAIDs are better than others, therefore the one that best fits the patient characteristics should be used. **[5, D]**

	Treatment for pain • Analgesics are indicated to control pain. If there is no response, surgical treatment can be considered, especially to restore function and mobility. **[5, D]**

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

Canadian Agency for Drugs and Technologies in Health (CADTH), 2015 [3]. Tofacitinib, Indication: Rheumatoid Arthritis: Common drug review, CDEC final recommendation	**TOFACITINIB (Xeljanz — Pfizer Canada Inc.)** Indication: Rheumatoid Arthritis Recommendation: The Canadian Drug Expert Committee (CDEC) recommends that tofacitinib be listed, in combination with methotrexate (MTX), for reducing the signs and symptoms of rheumatoid arthritis (RA) in adult patients with moderately to severely active RA or as monotherapy in those who were intolerant to MTX, if the following clinical criterion and conditions are met: Clinical criterion: • Inadequate response or intolerance to non-biologic disease-modifying antirheumatic drugs (DMARDs). • Conditions: • List in a similar manner to biologic DMARDs • Daily dosage not to exceed 10 mg (i.e., 5 mg twice daily) • Drug plan cost for tofacitinib not to exceed the drug plan costs for the biologic DMARDs reimbursed. Reasons for the Recommendation: 1. Five double-blind randomized controlled trials (RCTs) conducted in patients with active RA demonstrated that treatment with tofacitinib, with or without background DMARD therapy, was superior to placebo for achieving clinical response as measured using the American College of Rheumatology (ACR) 20, ACR 50, and ACR 70 criteria. 2. Similar to biologic DMARDs used to treat RA, tofacitinib is associated with an increased risk of harm, including malignancies and serious infections. 3. At the submitted price of $23.10 per 5 mg tablet ($46.19 per day), the CADTH Common Drug Review (CDR) estimates that treatment with tofacitinib is more costly than treatment with subsequent entry biologic infliximab (Inflectra), intravenous (IV) tocilizumab, and subcutaneous (SC) tocilizumab, with incremental costs ranging from $1,272 to $8,718 in the first year of treatment for patients weighing 70 kg.

Anlage 1

Patientenrelevante Endpunkte aus IQWiG 2013 [11]

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 [17]: 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 [1]*

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.

Anlage 4

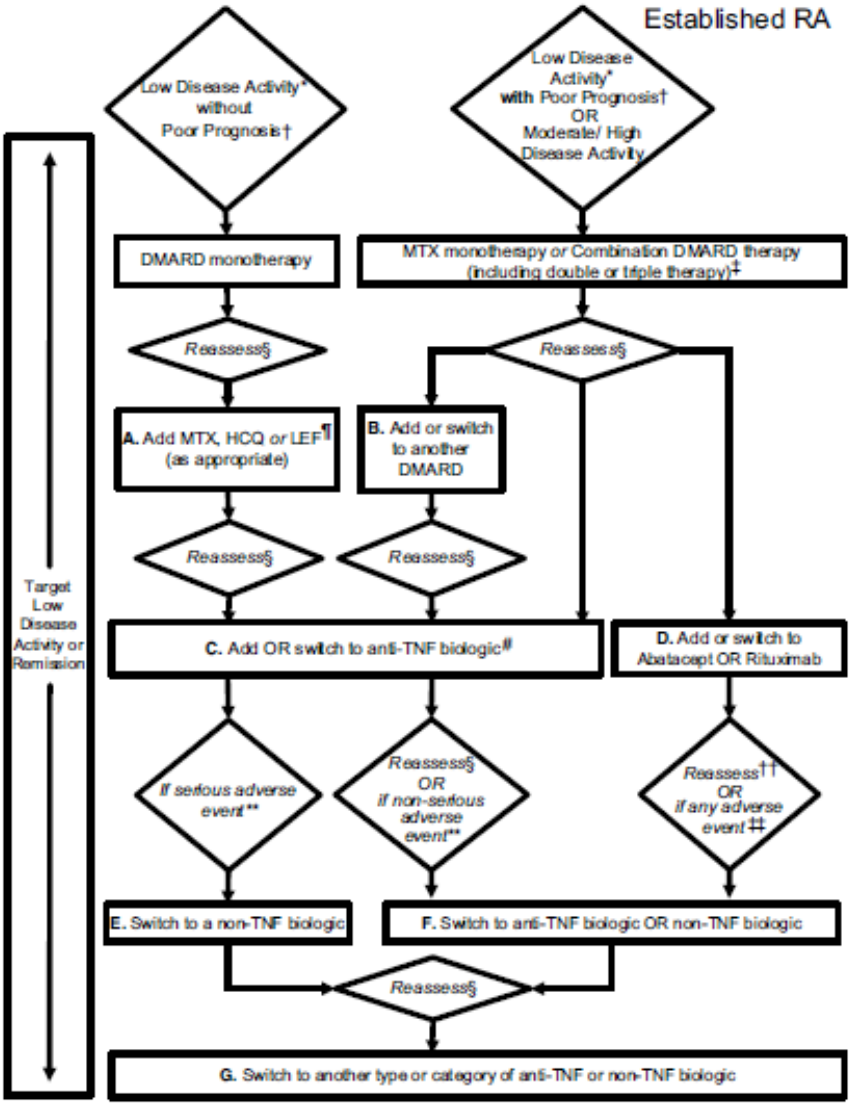


Figure 2. 2012 American College of Rheumatology (ACR) recommendations update for the treatment of established rheumatoid arthritis (RA), defined as a disease duration ≥6 months or meeting the 1987 ACR classification criteria. Depending on a patient's current medication regimen, the management algorithm may begin at an appropriate rectangle in the figure, rather than only at the top of the figure. Disease-modifying antirheumatic drugs (DMARDs) include hydroxychloroquine (HCQ), leflunomide (LEF), methotrexate (MTX), minocycline, and sulfasalazine (therapies are listed alphabetically; azathioprine and cyclosporine were considered but not included). DMARD monotherapy refers to treatment in most instances with HCQ, LEF, MTX, or sulfasalazine; in few instances, where appropriate, minocycline may also be used. Anti–tumor necrosis factor (anti-TNF) biologics include adalimumab, certolizumab pegol, etanercept, infliximab, and golimumab. Non-TNF biologics include abatacept, rituximab, or tocilizumab (therapies are listed alphabetically). For the level of evidence supporting each recommendation, please see Supplementary Appendix 7 (available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658).

* Definitions of disease activity are discussed in Tables 2 and 3 and Supplementary Appendix 4 (available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658) and were categorized as low, moderate, or high.

† Features of poor prognosis included the presence of 1 or more of the following: functional limitation (e.g., Health Assessment Questionnaire score or similar valid tools), extraarticular disease (e.g., presence of rheumatoid nodules, RA vasculitis, Felty's syndrome), positive rheumatoid factor or anti–cyclic citrullinated peptide antibodies (33–37), and bony erosions by radiograph (38).

‡ Combination DMARD therapy with 2 DMARDs, which is most commonly MTX based, with few exceptions (e.g., MTX + HCQ, MTX + LEF, MTX + sulfasalazine, sulfasalazine + HCQ), and triple therapy (MTX + HCQ + sulfasalazine).

§ Reassess after 3 months and proceed with escalating therapy if moderate or high disease activity in all instances except after treatment with a non-TNF biologic (rectangle D), where reassessment is recommended at 6 months due to a longer anticipated time for peak effect.

¶ LEF can be added in patients with low disease activity after 3–6 months of minocycline, HCQ, MTX, or sulfasalazine.

If after 3 months of intensified DMARD combination therapy or after a second DMARD has failed, the option is to add or switch to an anti-TNF biologic.

** Serious adverse events were defined per the US Food and Drug Administration (FDA; see below); all other adverse events were considered nonserious adverse events.

†† Reassessment after treatment with a non-TNF biologic is recommended at 6 months due to anticipation that a longer time to peak effect is needed for non-TNF compared to anti-TNF biologics.

‡‡ Any adverse event was defined as per the US FDA as any undesirable experience associated with the use of a medical product in a patient. The FDA definition of serious adverse event includes death, life-threatening event, initial or prolonged hospitalization, disability, congenital anomaly, or an adverse event requiring intervention to prevent permanent impairment or damage.

Detaillierte Darstellung der Recherchestrategie:

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) **am 19.12.2016**

#	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 2011 to 2016, in Cochrane Reviews (Reviews only) and Technology Assessments

SR, HTAs in Medline (PubMed) am 19.12.2016

#	Suchfrage
1	"arthritis, rheumatoid/therapy"[MeSH Major Topic]
2	(rheumatoid[Title/Abstract]) AND arthritis[Title/Abstract]
3	(rheumatoid[Title]) AND arthritis[Title]
4	((((((((((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 drug*[Title/Abstract]
5	((#2 AND #4)) NOT medline[sb]
6	(#3) AND #4
7	((#1) OR #5) OR #6
8	(Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp])
9	(((((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]))))
10	(#8) OR #9
11	(#7) AND #10
12	(#11) AND ("2011/12/01"[PDAT] : "2016/12/19"[PDAT])
13	(#12) NOT "The Cochrane database of systematic reviews"[Journal]

Leitlinien in Medline (PubMed) am 19.12.2016

#	Suchfrage
1	arthritis, rheumatoid[MeSH Terms]
2	(rheumatoid[Title/Abstract]) AND arthritis[Title/Abstract]
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]) OR recommendation*[Title]
5	(#3) AND #4
6	(#5) AND ("2011/12/01"[PDAT] : "2016/12/19"[PDAT])

Literatur

1. **Bykerk VP, Akhavan P, Hazlewood GS, Schieir O, Dooley A, Haraoui B, et al.** Canadian Rheumatology Association recommendations for pharmacological management of rheumatoid arthritis with traditional and biologic disease-modifying antirheumatic drugs. J Rheumatol 2012;39(8):1559-1582.

2. **Canadian Agency for Drugs and Technologies in Health (CADTH).** Biologic switching for patients with rheumatoid arthritis: a review of clinical effectiveness, safety, and guidelines [online]. Ottawa (CAN): CADTH; 2015. [Zugriff: 21.12.2016]. URL: https://www.cadth.ca/sites/default/files/pdf/htis/dec-2015/RC0732%20Biologic%20Switching%20in%20RA%20Final.pdf.

3. **Canadian Agency for Drugs and Technologies in Health (CADTH).** Tofacitinib, Indication: Rheumatoid Arthritis: Common drug review, CDEC final recommendation [online]. Ottawa (CAN): CADTH; 2015. [Zugriff: 21.12.2016]. URL: https://www.cadth.ca/sites/default/files/cdr/complete/cdr_complete_SR0380_Xeljanz_Apr-21-15.pdf.

4. **Chauffier K, Salliot C, Berenbaum F, Sellam J.** Effect of biotherapies on fatigue in rheumatoid arthritis: a systematic review of the literature and meta-analysis. Rheumatology (Oxford) 2012;51(1):60-68.

5. **Conway R, Low C, Coughlan RJ, O'Donnell MJ, Carey JJ.** Leflunomide Use and Risk of Lung Disease in Rheumatoid Arthritis: A Systematic Literature Review and Metaanalysis of Randomized Controlled Trials. J Rheumatol 2016;43(5):855-860.

6. **De Olivera Costa J, Lemos LL, Machado MA, Almeida AM, Kakehasi AM, Araujo VE, et al.** Infliximab, methotrexate and their combination for the treatment of rheumatoid arthritis: a systematic review and meta-analysis. Rev Bras Reumatol 2015;55(2):146-158.

7. **Donahue KE, Jonas DE, Hansen RA, Roubey R, Jonas B, Lux LJ, et al.** Drug Therapy for Rheumatoid Arthritis in Adults: An Update [online]. Rockville (USA): Agency for Healthcare Research and Quality; 2012. [Zugriff: 21.12.2016]. (Comparative Effectiveness Review; Band 55). URL: https://effectivehealthcare.ahrq.gov/ehc/products/203/1044/CER55_DrugTherapiesforRheumatoidArthritis_FinalReport_20120618.pdf.

8. **Guipcar Group.** Update of the clinical practice guideline for the management of rheumatoid arthritis in Spain [online]. Madrid (ESP): Spanish Society of Rheumatology; 2011. [Zugriff: 21.12.2016]. URL: http://www.ser.es/wp-content/uploads/2016/01/GUIPCAR_31Marzo2012_ENG.pdf.

9. **Hazlewood GS, Barnabe C, Tomlinson G, Marshall D, Devoe D, Bombardier C.** Methotrexate monotherapy and methotrexate combination therapy with traditional and biologic disease modifying antirheumatic drugs for rheumatoid arthritis: abridged Cochrane systematic review and network meta-analysis. BMJ 2016;353:i1777.

10. **Hazlewood GS, Barnabe C, Tomlinson G, Marshall D, Devoe DJ, Bombardier C.** Methotrexate monotherapy and methotrexate combination therapy with traditional and biologic disease modifying anti-rheumatic drugs for rheumatoid arthritis: A network meta-analysis. Cochrane Database of Systematic Reviews [online]. 2016(8):Cd010227. URL: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010227.pub2/abstract.

11. **Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG).** Biotechnologisch hergestellte Arzneimittel in der Zweitlinientherapie bei der rheumatoiden Arthritis; Abschlussbericht; Auftrag A10-01 [online]. Köln (GER): IQWiG; 28.06.2013. [Zugriff: 19.12.2016]. (IQWiG-Berichte; Band 180). URL: https://www.iqwig.de/download/A10-01_Abschlussbericht_Biologika-Zweitlinientherapie-bei-rheumatoider-Arthritis.pdf.

12. **Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG).** Biotechnologisch hergestellte Wirkstoffe bei rheumatoider Arthritis; Vorläufiger Berichtsplan; Auftrag A16-70 [online]. Köln (GER): IQWiG; 21.02.2017. [Zugriff: 04.05.2017]. URL: https://www.iqwig.de/download/A16-70_Biotechnologisch-hergestellte-Wirkstoffe-bei-rheumatoider-Arthritis_Vorlaeufiger-Berichtsplan_V1-0.pdf.

13. **Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG).** Systematische Leitlinienrecherche und -bewertung sowie Extraktion relevanter Empfehlungen für ein DMP Rheumatoide Arthritis; Abschlussbericht; Auftrag V14-02; Version 1.1 [online]. Köln (GER): IQWiG; 16.03.2016. [Zugriff: 19.12.2016]. (IQWiG-Berichte; Band 373). URL: https://www.iqwig.de/download/V14-02_Abschlussbericht_Version1-1_Leitlinienrecherche-und-bewertung-fuer-ein-DMP-Rheumatoide-Arthritis.pdf.

14. **Lethaby A, Lopez-Olivo MA, Maxwell LJ, Burls A, Tugwell P, Wells GA.** Etanercept for the treatment of rheumatoid arthritis. Cochrane Database of Systematic Reviews [online]. 2013(5):Cd004525. URL: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004525.pub2/abstract.

15. **Lopez-Olivo MA, Amezaga UM, McGahan L, Pollono EN, Suarez-Almazor ME.** Rituximab for rheumatoid arthritis. Cochrane Database of Systematic Reviews [online]. 2015(1):Cd007356. URL: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007356.pub2/abstract.

16. **Malottki K, Barton P, Tsourapas A, Uthman AO, Liu Z, Routh K, et al.** Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor: a systematic review and economic evaluation. Health Technol Assess 2011;15(14):1-300.

17. **Michaud TL, Rho YH, Shamliyan T, Kuntz KM, Choi HK.** The comparative safety of tumor necrosis factor inhibitors in rheumatoid arthritis: a meta-analysis update of 44 trials. Am J Med 2014;127(12):1208-1232.

18. **National Institute for Health and Care Excellence (NICE).** Rheumatoid arthritis in adults: management [online]. Last updated: 12.2015. London (GBR): NICE; 02.2009. [Zugriff: 19.12.2016]. (Clinical guideline; Band 79). URL: https://www.nice.org.uk/guidance/cg79/resources/rheumatoid-arthritis-in-adults-management-975636823525.

19. **Navarro-Millan I, Singh JA, Curtis JR.** Systematic review of tocilizumab for rheumatoid arthritis: a new biologic agent targeting the interleukin-6 receptor. Clin Ther 2012;34(4):788-802 e783.

20. **Orme ME, Macgilchrist KS, Mitchell S, Spurden D, Bird A.** Systematic review and network meta-analysis of combination and monotherapy treatments in disease-modifying antirheumatic drug-experienced patients with rheumatoid arthritis: analysis of American College of Rheumatology criteria scores 20, 50, and 70. Biologics 2012;6:429-464.

21. **Pierreisnard A, Issa N, Barnetche T, Richez C, Schaeverbeke T.** Meta-analysis of clinical and radiological efficacy of biologics in rheumatoid arthritis patients naive or inadequately responsive to methotrexate. Joint Bone Spine 2013;80(4):386-392.

22. **Ruiz GV, Jobanputra P, Burls A, Cabello JB, Vela CP, Bort-Marti S, et al.** Certolizumab pegol (CDP870) for rheumatoid arthritis in adults. Cochrane Database of Systematic Reviews [online]. 2014(9):Cd007649. URL: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007649.pub3/abstract.

23. **Schoels MM, van der Heijde D, Breedveld FC, Burmester GR, Dougados M, Emery P, et al.** Blocking the effects of interleukin-6 in rheumatoid arthritis and other inflammatory rheumatic diseases: systematic literature review and meta-analysis informing a consensus statement. Ann Rheum Dis 2013;72(4):583-589.

24. **Scott DL, Ibrahim F, Farewell V, O'Keeffe AG, Ma M, Walker D, et al.** 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 and associated systematic reviews. Health Technol Assess 2014;18(66):i-xxiv, 1-164.

25. **Scottish Intercollegiate Guidelines Network (SIGN).** Management of early rheumatoid arthritis [online]. Edinburgh (GBR): SIGN; 2011. [Zugriff: 19.12.2016]. (SIGN publication; Band 123). URL: http://www.sign.ac.uk/pdf/sign123.pdf.

26. **Singh JA, Cameron C, Noorbaloochi S, Cullis T, Tucker M, Christensen R, et al.** Risk of serious infection in biological treatment of patients with rheumatoid arthritis: a systematic review and meta-analysis. Lancet 2015;386(9990):258-265.

27. **Singh JA, Hossain A, Tanjong GE, Kotb A, Christensen R, Mudano AS, et al.** 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. Cochrane Database of Systematic Reviews [online]. 2016(5):Cd012183. URL: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD012183/abstract.

28. **Singh JA, Hossain A, Tanjong GE, Mudano AS, Tugwell P, Wells GA.** Biologic or tofacitinib monotherapy for rheumatoid arthritis in people with traditional disease-modifying anti-rheumatic drug (DMARD) failure: a Cochrane Systematic Review and network meta-analysis (NMA). Cochrane Database of Systematic Reviews [online]. 2016(11):Cd012437. URL: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD012437/abstract.

29. **Singh JA, Saag KG, Bridges SL, Akl EA, Bannuru RR, Sullivan MC, et al.** 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Care Res (Hoboken) 2016;68(1):1-25.

30. **Smolen JS, Landewe R, Breedveld FC, Buch M, Burmester G, Dougados M, et al.** EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis 2014;73(3):492-509.

31. **Song GG, Bae SC, Lee YH.** Efficacy and safety of tofacitinib for active rheumatoid arthritis with an inadequate response to methotrexate or disease-modifying antirheumatic drugs: a meta-analysis of randomized controlled trials. Korean J Intern Med 2014;29(5):656-663.

32. **Stevenson M, Archer R, Tosh J, Simpson E, Everson-Hock E, Stevens J, et al.** Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept 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. Health Technol Assess 2016;20(35):1-610.

33. **Teitsma XM, Marijnissen AK, Bijlsma JW, Lafeber FP, Jacobs JW.** Tocilizumab as monotherapy or combination therapy for treating active rheumatoid arthritis: a meta-analysis of efficacy and safety reported in randomized controlled trials. Arthritis Res Ther 2016;18(1):211.

34. **Thaler KJ, Gartlehner G, Kien C, Van Noord MG, Thakurta S, Wines RCM, et al.** Drug Class Review: Targeted Immune Modulators: Final Update 3 Report. Portland (USA); Oregon Health and Science University; 2012.

35. **Zhang X, Liang F, Yin X, Xiao X, Shi P, Wei D, et al.** Tofacitinib for acute rheumatoid arthritis patients who have had an inadequate response to disease-modifying antirheumatic drug (DMARD): a systematic review and meta-analysis. Clin Rheumatol 2014;33(2):165-173.