Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: Filgotinib

Stand: Juni 2019

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

Filgotinib [rheumatoide 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	Beschlüsse zur Nutzenbewertung nach §35a SGB V • Beschluss zu Baricitinib vom 21. September 2017 • Beschluss zu Tofacitinib vom 19. Oktober 2017 bzw. 1. November 2018 • Beschluss zu Sarilumab vom 15. Februar 2018 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. August 2013 Therapiehinweise gemäß § 92 Abs. 2 Satz 7 SGB V i. V. m. § 17 Arzneimittel-Richtlinie (AM-RL) zu • Adalimumab, Infliximab, Leflunomid IQWiG-Beauftragung zu Nutzenbewertung von biotechnologisch hergestellten Wirkstoffen zur Behandlung der rheumatoiden Arthritis ; IQWiG-Vorbericht A16-70 vom 6. Juni 2018
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Filgotinib	
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

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	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 (…) 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	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:

II. Zugelassene Arzneimittel im Anwendungsgebiet	
generisch	- 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 Deximune®	Rheumatoide Arthritis: Behandlung von schwerer, aktiver rheumatoider Arthritis. […] (Stand: Dezember 2015)
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

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	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)
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)
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

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	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)
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)
Weitere gezielte Therapien: **tsDMARDs**	
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 werden.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	(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)

Quellen: Lauer-Fischer; AMIS; Fachinformation

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2019-B-105 (Filgotinib)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	6. Juni 2019

Inhaltsverzeichnis

Abkürzungsverzeichnis

ABAT	Abatacept
ABT	Abatacept
ACR	American College of Rheumatology
ADA	Adalimumab
ADL	Adalimumab
AWMF	The Association of the Scientific Medical Societies in Germany (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften)
AZA	Azathioprine
bDMARD	biological DMARD
CI	Confidence interval
CQ	Chloroquine
csDMARD	conventional synthetic DMARD
CTZ	Certolizumab
CyA	Cyclosporine
DMARD	Disease-modifying antirheumatic drug
ETN	Etanercept
EULAR	European League Against Rheumatism
G-BA	Federal Joint Committee (Gemeinsamer Bundesausschuss)
GIN	Guidelines International Network
GOL	Golimumab
GoR	Grade of Recommendations
HCQ	Hydroxychloroquine
HR	Hazard ratio
IFX	Infliximab
IM	intra-muscular
INF	Infliximab
IQWiG	Institute for Quality and Efficiency in Healthcare (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen)
IV	intravenous
LEF	Leflunomide
LFN	Leflunomide

LoE	Level of Evidence
MTX	Methotrexate
NICE	National Institute for Health and Care Excellence
OR	Odds ratio
RA	Rheumatoid arthritis
RTX	Rituximab
Sc	subcutaneous
SIGN	Scottish Intercollegiate Guidelines Network
SSZ	Sulphasalazine
TCZ	Tocilizumab
TOFA	Tofacitinib
TRIP	Turn Research into Practice Database
tsDMARD	targeted synthetic DMARD
WHO	World Health Organization

1 Indikation

zur Behandlung von mittelschwerer bis schwerer rheumatoiden Arthritis (RA) bei erwachsenen Patienten, die unzureichend oder mit einer Unverträglichkeit auf ein oder mehrere krankheitsmodifizierende Antirheumatika (DMARDs) angesprochen haben.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *rheumatoide Arthritis* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 07.05.2019 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, G-BA, GIN, IQWIG, 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 1567 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. Insgesamt ergab dies 30 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

3 Ergebnisse

3.1 G-BA-Beschlüsse/IQWiG-Berichte

G-BA, 2018 [11].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Sarilumab

Indikation

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.

Zweckmäßige Vergleichstherapie

Sarilumab in Monotherapie und in Kombinationstherapie mit MTX für

a) Patienten, bei denen keine ungünstigen Prognosefaktoren1 vorliegen und die unzureichend auf eine vorangegangene Behandlung mit einem krankheitsmodifizierenden Antirheumatikum (klassische DMARDs, inklusive Methotrexat (MTX)) ansprachen oder diese nicht vertragen haben:

Zweckmäßige Vergleichstherapie:

Alternative klassische DMARDs, sofern geeignet (z. B. MTX, Leflunomid) als Mono- oder Kombinationstherapie

Sarilumab in Monotherapie und in Kombinationstherapie mit MTX für

b) bDMARD-naive Patienten, für die eine erstmalige Therapie mit bDMARDs angezeigt ist:

b1) Sarilumab in Monotherapie (wenn MTX nicht vertragen wird oder eine Behandlung mit MTX ungeeignet ist)

Zweckmäßige Vergleichstherapie:

biotechnologisch hergestellte DMARDs (bDMARDs) (Adalimumab oder Etanercept oder Certolizumab-Pegol oder Tocilizumab) als Monotherapie unter Berücksichtigung des jeweiligen Zulassungsstatus bei MTX-Unverträglichkeit

b2) Sarilumab in Kombinationstherapie mit MTX

Zweckmäßige Vergleichstherapie:

biotechnologisch hergestellte DMARDs (bDMARDs) in Kombination mit MTX (Adalimumab oder Etanercept oder Certolizumab-Pegol oder Golimumab oder Abatacept oder Tocilizumab)

Sarilumab in Monotherapie und in Kombinationstherapie mit MTX für

c) Patienten, die unzureichend auf eine vorangegangene Behandlung mit einem oder mehreren bDMARDs ansprachen oder diese nicht vertragen haben:

Zweckmäßige Vergleichstherapie:

Wechsel der bDMARD-Therapie (Adalimumab oder Etanercept oder Certolizumab-Pegol oder Golimumab oder Abatacept oder Tocilizumab; in Kombination mit MTX; ggf. als Monotherapie unter Berücksichtigung des jeweiligen Zulassungsstatus bei MTX-Unverträglichkeit; oder bei Patienten mit schwerer rheumatoider Arthritis Rituximab unter Berücksichtigung der Zulassung) in Abhängigkeit von der Vortherapie.

Ausmaß des Zusatznutzens

a) Ein Zusatznutzen ist nicht belegt.

b1) Anhaltspunkt für einen beträchtlichen Zusatznutzen gegenüber Adalimumab.

b2) Ein Zusatznutzen ist nicht belegt.

c) Ein Zusatznutzen ist nicht belegt.

G-BA, 2017 [12].

Geltende Fassung zum Beschluss vom 19. Oktober 2017 – Tofacitinib

Siehe auch [10]:

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AMRL): Anlage XII – Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Tofacitinib (Neubewertung nach Fristablauf)

Indikation

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.

Zweckmäßige Vergleichstherapie

<u>Tofacitinib in Monotherapie und in Kombinationstherapie mit MTX für</u>

a) Patienten, bei denen keine ungünstigen Prognosefaktoren[1] vorliegen und dieunzureichend auf eine vorangegangene Behandlung mit einemkrankheitsmodifizierenden Antirheumatikum (klassische DMARDs, inklusive Methotrexat(MTX)) ansprachen oder diese nicht vertragen haben:

[1] Ungünstige Prognosefaktoren:
- Nachweis von Autoantikörpern (z.B. Rheumafaktoren, hohe Spiegel von Antikörpern gegen citrullinierte Peptid-Antigene)
- Hohe Krankheitsaktivität (nachgewiesen durch DAS bzw. DAS28-Bewertungssystem, geschwollene Gelenke, Parameter der Akute-Phase-Reaktion wie z.B. C-Reaktives Protein, Erythrozytensedimentationsrate)
- Frühes Auftreten von Gelenkerosionen

Zweckmäßige Vergleichstherapie:

Alternative klassische DMARDs, sofern geeignet (z. B. MTX, Leflunomid) als Mono- oder Kombinationstherapie

Tofacitinib in Monotherapie und in Kombinationstherapie mit MTX für

b) bDMARD-naive Patienten, für die eine erstmalige Therapie mit bDMARDS angezeigt ist:

b1) Tofacitinib in Monotherapie (wenn MTX nicht vertragen wird oder eine Behandlung mit MTX ungeeignet ist)

Zweckmäßige Vergleichstherapie:

biotechnologisch hergestellte DMARDs (bDMARDs) (Adalimumab oder Etanercept oder Certolizumab-Pegol oder Tocilizumab) als Monotherapie unter Berücksichtigung des jeweiligen Zulassungsstatus bei MTX-Unverträglichkeit

b2) Tofacitinib in Kombinationstherapie mit MTX

Zweckmäßige Vergleichstherapie:

biotechnologisch hergestellte DMARDs (bDMARDs) in Kombination mit MTX (Adalimumab oder Etanercept oder Certolizumab-Pegol oder Golimumab oder Abatacept oder Tocilizumab)

Tofacitinib in Monotherapie und in Kombinationstherapie mit MTX für

c) Patienten, die unzureichend auf eine vorangegangene Behandlung mit einem oder mehreren bDMARDs ansprachen oder diese nicht vertragen haben:

Zweckmäßige Vergleichstherapie:

Wechsel der bDMARD-Therapie (Adalimumab oder Etanercept oder Certolizumab-Pegol oder Golimumab oder Abatacept oder Tocilizumab; in Kombination mit MTX; ggf. als Monotherapie unter Berücksichtigung des jeweiligen Zulassungsstatus bei MTX-Unverträglichkeit; oder bei Patienten mit schwerer rheumatoider Arthritis Rituximab unter Berücksichtigung der Zulassung) in Abhängigkeit von der Vortherapie.

Ausmaß des Zusatznutzens

a) Ein Zusatznutzen ist nicht belegt.

b1) Ein Zusatznutzen ist nicht belegt gegenüber Adalimumab.

b2) Ein Zusatznutzen ist nicht belegt gegenüber Adalimumab + MTX.

b) Ein Zusatznutzen ist nicht belegt.

G-BA, 2017[13].

Geltende Fassung zum Beschluss vom 21. September 2017 – Baricitinib

Indikation

Baricitinib (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 werden.

Zweckmäßige Vergleichstherapie

Baricitinib in Monotherapie und in Kombinationstherapie mit MTX für

a) Patienten, bei denen keine ungünstigen Prognosefaktoren[1] vorliegen und die unzureichend auf eine vorangegangene Behandlung mit einemkrankheitsmodifizierenden

Antirheumatikum (klassische DMARDs, inklusive Methotrexat (MTX)) ansprachen oder diese nicht vertragen haben:

[1] Ungünstige Prognosefaktoren:
- Nachweis von Autoantikörpern (z.B. Rheumafaktoren, hohe Spiegel von Antikörpern gegen citrullinierte Peptid-Antigene)
- Hohe Krankheitsaktivität (nachgewiesen durch DAS bzw. DAS28-Bewertungssystem, geschwollene Gelenke, Parameter der Akute-Phase-Reaktion wie z.B. C-Reaktives Protein, Erythrozytensedimentationsrate)
- Frühes Auftreten von Gelenkerosionen

Zweckmäßige Vergleichstherapie:

Alternative klassische DMARDs, sofern geeignet (z. B. MTX, Leflunomid) als Mono- oder Kombinationstherapie

Baricitinib in Monotherapie und in Kombinationstherapie mit MTX für

b) bDMARD-naive Patienten, für die eine erstmalige Therapie mit bDMARDs angezeigt ist:

b1) Baricitinib in Monotherapie

Zweckmäßige Vergleichstherapie:

biotechnologisch hergestellte DMARDs (bDMARD) in Kombination mit MTX (Adalimumab oder Etanercept oder Certolizumab-Pegol oder Golimumab oder Abatacept oder Tocilizumab); ggf. als Monotherapie unter Berücksichtigung des jeweiligen Zulassungsstatus bei MTX-Unverträglichkeit

b2) Baricitinib in Kombinationstherapie mit MTX

Zweckmäßige Vergleichstherapie:

biotechnologisch hergestellte DMARDs (bDMARDs) in Kombination mit MTX (Adalimumab oder Etanercept oder Certolizumab-Pegol oder Golimumab oder Abatacept oder Tocilizumab)

c) Patienten, die unzureichend auf eine vorangegangene Behandlung mit einem oder mehreren bDMARDs ansprachen oder diese nicht vertragen haben:

Zweckmäßige Vergleichstherapie:

Wechsel der bDMARD – Therapie (Adalimumab oder Etanercept oder Certolizumab-Pegol oder Golimumab oder Abatacept oder Tocilizumab; in Kombination mit MTX; ggf. als Monotherapie unter Berücksichtigung des jeweiligen Zulassungsstatus bei MTX-Unverträglichkeit; oder bei Patienten mit schwerer rheumatoider Arthritis Rituximab unter Berücksichtigung der Zulassung) in Abhängigkeit von der Vortherapie. Je nach Vortherapie sollte ein Wechsel des Wirkprinzips erwogen werden.

Ausmaß des Zusatznutzens

a) Ein Zusatznutzen ist nicht belegt.

b1) Ein Zusatznutzen ist nicht belegt gegenüber Adalimumab.

b2) Ein Zusatznutzen ist nicht belegt gegenüber Adalimumab + MTX.

c) Ein Zusatznutzen ist nicht belegt.

G-BA, 2016 [14].

Therapiehinweise gemäß § 92 Abs. 2 Satz 7 SGB V i. V. m. § 17 AM-RL zur wirtschaftlichen Verordnungsweise von Arzneimitteln

Adalimumab

(Humira®)

Beschluss vom: 21.11.2006

In Kraft getreten am: 12.07.2007

BAnz. 2007 Nr. 126; 11. Juli 2007, S. 6932

Bei Rheumatoider Arthritis und Psoriasis-Arthritis (Arthritis psoriatica)

Empfehlungen zur wirtschaftlichen Verordnungsweise

Patienten mit Rheumatoider Arthritis (RA) sollen möglichst früh mit Disease Modifying Antirheumatic Drugs (DMARDs = „Basistherapeutika“) behandelt werden. Es gibt Hinweise darauf, dass hierdurch die Prognose der RA günstig beeinflusst wird und dass dieses Vorgehen entscheidend zum Erhalt der Funktion und zur Verminderung späterer Funktionseinschränkungen beiträgt.

Die Behandlung mit TNF-alpha-Hemmern stellt dabei eine Alternative zur Reduktion der Symptomatik und Verbesserung der körperlichen Funktionsfähigkeit bei Patienten mit aktiver Rheumatoider Arthritis oder Arthritis psoriatica dar, wenn eine Therapie mit allen individuell indizierten DMARDs und deren Kombinationen, mindestens jedoch 2 einschließlich Methotrexat (MTX) - soweit keine Kontraindikationen dafür vorliegen - bis zur individuell angezeigten Höchstdosis (in der Regel 20 bis 25 mg pro Woche, ggf. als Injektion und ggf. Folsäure- bzw. Folinsäurepräparate), erfolglos geblieben ist. Diese müssen lange genug (in der Regel je nach DMARD mindestens jeweils 3 bis 6 Monate) in adäquater Dosis und unter fachlich kompetenter Überwachung eingesetzt worden sein.

[…] In der Regel ist die Primäranwendung daher bei der derzeitigen Studienlage nicht angezeigt. Bei seltenen individuellen Besonderheiten (Kontraindikationen gegen alle DMARDs oder hohe Krankheitsprogression) kann ein frühzeitiger Einsatz von TNF-alpha-Hemmern angemessen sein.

Bei der Wahl eines TNF-alpha-Hemmers können aus medizinisch-therapeutischer Sicht aufgrund der derzeitigen Studienlage oder evidenzbasierter Leitlinien bei der Indikation Rheumatoide Arthritis keine allgemeinen Prioritäten gesetzt werden. […] Die voraussichtlichen Therapiekosten für das ausgewählte Präparat stellen damit bei Beginn einer TNF-alpha-Therapie den wesentlichen Gesichtspunkt bei der Produktwahl dar. Davon kann abgewichen werden, wenn individuelle klinische Faktoren (z.B. Neben- und Wechselwirkungen) bzw. die spezifischen Eigenschaften oder die Anwendungsmodalitäten des Arzneimittels eine nachvollziehbare Kontraindikation darstellen oder die bevorzugte Anwendung im Einzelfall begründen. Auch die Praxisausstattung (z.B. Lagerungsmöglichkeit für Infusionen und Nachüberwachung beim Einsatz von Infliximab) begründet keine unwirtschaftliche Produktwahl.

Ein Ansprechen auf die Therapie ist bereits nach 1 bis 2 Wochen zu erwarten. Soweit auch nach 3 Monaten kein deutliches klinisches Ansprechen (klinische Symptomatik, DAS-Score, Labor) zu verzeichnen ist, ist die Therapie mit Adalimumab abzusetzen.

[…]

Infliximab bei Rheumatoider Arthritis

(z.B. Remicade®)

Beschluss vom: 26.02.2002

In Kraft getreten am: 22.06.2002

BAnz. 2002, Nr. 112 vom 21.06.2002, S. 13 577

Empfehlungen zur wirtschaftlichen Verordnungsweise

Die Behandlung mit Infliximab stellt eine Alternative zur Reduktion der Symptomatik und Verbesserung der körperlichen Funktionsfähigkeit bei Patienten mit aktiver rheumatoider Arthritis dar, wenn eine Therapie mit allen individuell indizierten DMARD´s (“ Basistherapeutika”) einschließlich MTX bis zu einer Dosis von 25 mg pro Woche (+ ggf. Folinsäure) und deren Kombinationen erfolglos geblieben ist (Smolen 1999, Furst 2000). Diese müssen lang genug (in der Regel mindestens 6 Monate), in adäquater Dosis und unter fachlich kompetenter Überwachung eingesetzt worden sein (Empf.)

[…]

Infliximab muss zusammen mit MTX verabreicht werden. Soweit eine Indikation für eine Therapie mit einem TNF alpha-Hemmer besteht und keine gesicherte Kontraindikation für MTX oder Infliximab vorliegt, ist derzeit eine Prioritätensetzung aufgrund der Studienlage nicht möglich (Klippel). Damit stellt die Wirtschaftlichkeit einen wesentlichen Gesichtspunkt bei der Produktwahl dar. Die Praxisausstattung (Unterbringung für die 2stündige Infusion und die 1-2stündige Nachüberwachung) begründet keine unwirtschaftliche Produktwahl.

Die Therapie ist zu beenden, wenn nach 8 - 12 Wochen keine signifikante Besserung der klinischen und humoralen Entzündungsaktivität zu verzeichnen ist (Furst).

[…]

Leflunomid

(z. B. Arava®)

Beschluss vom: 16.08.2007 / 15.05.2008

In Kraft getreten am: 21.12.2007 / 03.09.2008

BAnz. 2007, Nr. 238 vom 20.12.2007, S. 8 316 / BAnz. 2008, Nr. 132 vom 02.09.2008, S. 3 216

Empfehlungen zur wirtschaftlichen Verordnungsweise

Rheumatoide Arthritis

Patienten mit rheumatoider Arthritis (RA) sollten möglichst frühzeitig mit Basistherapeutika (Basistherapeutikum = Disease Modifying Antirheumatic Drug = DMARD) behandelt werden, um die Entwicklung von Funktionseinschränkungen zu vermeiden.

Ein engmaschiges Monitoring der Krankheitsaktivität unter Therapie mit DMARDs ist wichtig für die Prognose der Erkrankung. Ein unzureichendes Ansprechen sollte umgehend zu Therapie-Modifikationen führen.

[…]

In fortgeschritteneren Krankheitsstadien hat sich Leflunomid als ähnlich wirksam erwiesen wie MTX oder SSZ (s.u. Abschnitt Wirksamkeit). Unter wirtschaftlichen Gesichtspunkten bietet es sich als Mittel der zweiten oder dritten Wahl an.

Bei therapierefraktären Verläufen kann sein Einsatz erwogen werden bevor auf einen TNF Alpha Blocker umgestellt wird.

Die Überlegenheit einer Kombination von Leflunomid mit einem Tumornekrosefaktor (TNF) Alpha Blocker gegenüber einer TNF Alpha Blocker Monotherapie ist durch randomisierte kontrollierte Studien nicht belegt. Vergleichende Studien zur Kombination von TNF Alpha Blockern mit MTX gibt es nicht. Es ist bisher kein TNF Alpha Blocker explizit für eine Kombinationstherapie mit Leflunomid zugelassen.

Bei ungesichertem Nutzen und erhöhtem Risiko für toxische Nebenwirkungen ist eine Kombinationstherapie von Leflunomid mit TNF Alpha Blockern in der Regel unwirtschaftlich. Für den Fall einer Unverträglichkeit von MTX auch in niedrigeren Dosierungen bzw. Vorliegen von Kontraindikationen, die den Einsatz von MTX ausschließen, sind die TNF Alpha Inhibitoren Adalimumab und Etanercept auch als Monotherapie zugelassen. Bei Versagen einer Therapie mit TNF Alpha Blockern stehen für diese Situation zugelassene Biologicals wie Abatacept oder Rituximab zur Verfügung.

IQWiG, 2018 [17].

Biotechnologisch hergestellte Wirkstoffe bei rheumatoider Arthritis - Vorbericht (vorläufige Nutzenbewertung)

Auftrag: A16-70

Version: 1.0

Stand: 30.05.2018

Fragestellung

Das Ziel der vorliegenden Untersuchung ist

- die Nutzenbewertung von Biologika im Vergleich untereinander bei Patientinnen und Patienten mit rheumatoider Arthritis hinsichtlich patientenrelevanter Endpunkte.

Methoden

Die Zielpopulation der Nutzenbewertung bildeten erwachsene Patientinnen und Patienten (≥ 18 Jahre) mit rheumatoider Arthritis. Alle zum Zeitpunkt der Beauftragung durch den G-BA zugelassenen Biologika sollten untereinander verglichen werden und waren damit sowohl Prüf- als auch Vergleichsintervention.

[…]

Es wurden ausschließlich randomisierte kontrollierte Studien (RCTs) mit einer Mindestdauer von 6 Monaten (24 Wochen) in die Nutzenbewertung eingeschlossen.

Eine systematische Literaturrecherche […] wurde in den Datenbanken MEDLINE, Embase und Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects und Health Technology Assessment Database [durchgeführt].

Die letzte Suche fand am 02.03.2017 statt.

Darüber hinaus wurden folgende Informationsquellen und Suchtechniken berücksichtigt: Studienregister, Dokumente von Herstellerfirmen, öffentlich zugängliche Dokumente von Zulassungsbehörden, die Website des G-BA und des Instituts für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG), die Sichtung von Referenzlisten, aus Anhörungsverfahren zur Verfügung gestellte Dokumente und Autorenanfragen.

[…] Zur Einschätzung der qualitativen Ergebnissicherheit wurde das Verzerrungspotenzial auf Studien- und Endpunktebene bewertet und jeweils in niedrig oder hoch eingestuft. Für Studien, deren Kontrollintervention ausschließlich als Brückenkomparator in eine Netzwerk-Metaanalyse (NMA) einging, wurde das Verzerrungspotenzial nur bewertet, wenn es als Faktor bei Überprüfung der Strukturqualität zu untersuchen war oder wenn es zur Ableitung der Beleglage ausschlaggebend war (Vorliegen eines statistisch signifikanten Unterschieds auf Basis eines indirekten Vergleichs, bei dem für eines der oder beide Biologika nur 1 Studie vorlag). […]

Da das Ziel der vorliegenden Nutzenbewertung der Vergleich der Biologika untereinander war, wurden ausschließlich NMAs berechnet, in denen mindestens 50 % der für eine Teilfragestellung zugelassenen Biologika abgebildet waren.

Die Einzelergebnisse wurden mithilfe von NMA analysiert, sofern für die Studien innerhalb der jeweiligen Teilfragestellungen eine ausreichende Strukturqualität vorlag, das heißt, die Annahmen von Ähnlichkeit, Homogenität und Konsistenz waren erfüllt oder nicht offensichtlich verletzt […]

Fazit

Kombinationstherapie mit Methotrexat nach Methotrexat-Versagen (Teilfragestellung 4)

In der Kombinationstherapie mit Methotrexat nach Methotrexat-Versagen wurden in der vorliegenden Nutzenbewertung folgende Biologika untereinander verglichen: Abatacept, Adalimumab, Anakinra, Certolizumab Pegol, Etanercept, Golimumab, Infliximab und Tocilizumab. Es lagen nur 2 Studien mit einem direkten Vergleich von Biologika vor. Für Tocilizumab gingen keine Daten in die Netzwerk-Metaanalysen ein, weil die entsprechenden Studien für dieses Biologikum in den Analyseschritten vor Durchführung der Netzwerk-Metaanalyse ausgeschlossen wurden.

Die Beleglage ist wie folgt:

- In der Kombinationstherapie mit Methotrexat nach Methotrexat-Versagen besteht für das primäre Therapieziel der klinischen Remission für Abatacept, Adalimumab, Certolizumab Pegol und Golimumab gegenüber Anakinra jeweils ein Anhaltspunkt für einen höheren Nutzen.
- Für Abatacept, Adalimumab und Infliximab gegenüber Anakinra gibt es jeweils einen Anhaltspunkt für einen höheren Nutzen für den Endpunkt niedrige Krankheitsaktivität.
- Für die gesundheitsbezogene Lebensqualität (körperlicher Summenscore des Short Form 36 – Health Survey) gibt es einen Anhaltspunkt für einen höheren Nutzen von Golimumab gegenüber Anakinra.
- Für Certolizumab Pegol gibt es gegenüber allen Biologika, abgesehen von Tocilizumab und Etanercept, einen Anhaltspunkt für einen höheren Schaden für die Endpunkte schwerwiegendes unerwünschtes Ereignis, Abbruch wegen unerwünschtem Ereignis, Infektionen und / oder schwerwiegende Infektionen.
- Darüber hinaus zeigt sich für Adalimumab sowie Golimumab jeweils gegenüber Infliximab ein Anhaltspunkt für einen höheren Schaden für den Endpunkt schwerwiegende Infektionen.
- Für alle weiteren Endpunkte gibt es für keines der Biologika gegenüber einem anderen Biologikum einen Anhaltspunkt für einen höheren oder geringeren Nutzen beziehungsweise Schaden in der Kombinationstherapie mit Methotrexat nach Methotrexat-Versagen.

Kombinationstherapie mit Methotrexat nach Biologikum-Versagen (Teilfragestellung 6)

In der Kombinationstherapie mit Methotrexat nach Biologikum-Versagen wurden in der vorliegenden Nutzenbewertung folgende Biologika untereinander verglichen: Adalimumab, Certolizumab Pegol, Golimumab, Rituximab und Tocilizumab. Für Abatacept, Anakinra, Etanercept und Infliximab wurden keine relevanten Studien identifiziert, sodass kein Vergleich mit den anderen Biologika möglich war. Zudem war der Studienpool mit insgesamt nur 5

Studien sehr klein. Unter diesen Studien gab es 1 Studie mit einem direkten Biologikavergleich. Ausschließlich für die Endpunkte klinische Remission und niedrige Krankheitsaktivität lagen Daten für mehr als die Hälfte der relevanten Biologika vor, sodass nur für diese Endpunkte NMAs gerechnet wurden.

Die Beleglage ist wie folgt:

- Für keines der Biologika gibt es für das primäre Therapieziel der klinischen Remission oder für einen anderen Endpunkt einen Anhaltspunkt für einen höheren oder geringeren Nutzen beziehungsweise Schaden gegenüber einem anderen Biologikum.

Weitere Teilfragestellungen

Für folgende Teilfragestellungen der vorliegenden Nutzenbewertung wurde aufgrund der unzureichenden Datenlage kein Fazit gezogen:

- Kombinationstherapie mit Methotrexat nach Methotrexat-Versagen und Vorbehandlung mit weiteren konventionellen, synthetisch hergestellten krankheitsmodifizierenden Antirheumatika (Teilfragestellung 2)
- Monotherapie nach Methotrexat-Unverträglichkeit und Vorbehandlung mit weiteren konventionellen, synthetisch hergestellten krankheitsmodifizierenden Antirheumatika (Teilfragestellung 3)
- Monotherapie nach Methotrexat-Unverträglichkeit (Teilfragestellung 5)
- Monotherapie nach Methotrexat-Unverträglichkeit und Biologikum-Versagen (Teilfragestellung 7)

IQWiG, 2013 [16].

Biotechnologisch hergestellte Arzneimittel in der Zweitlinientherapie bei der rheumatoiden Arthritis. Abschlussbericht.

IQWiG-Berichte – Nr. 180

Version: A10-01

Stand: 1.0

Auftrag: 28.06.2013

Fragestellung

Ziele der vorliegenden Untersuchung waren

- 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 sowie
- die Nutzenbewertung einer Behandlung mit biotechnologisch hergestellten Arzneimitteln im Vergleich zu einer Behandlung ohne Therapieerweiterung (mit oder ohne Placebokontrolle),

jeweils als Zweitlinientherapie bei Patienten mit rheumatoider Arthritis hinsichtlich patientenrelevanter Endpunkte.

Methoden

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:

- 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]	MTX[c]	1	41
(Patienten mit schwerer aktiver und progressiver RA)			
Golimumab	Placebo	2	401
(keine Vorbehandlung mit TNF-α-Inhibitoren)			
	Placebo	1	205
(Vorbehandlung mit TNF-α-Inhibitoren)			
Infliximab	Placebo	1	174
Rituximab	Placebo	1	520
(keine Vorbehandlung mit Rituximab)			
	Placebo	1	475
(nach fehlendem Ansprechen auf einen Zyklus Rituximab)			
Tocilizumab	Placebo	5	2836
(mehrheitlich ohne Vorbehandlung mit TNF-α-Inhibitoren)			
	Placebo	1	335
(Vorbehandlung mit TNF-α-Inhibitoren)			
Direktvergleich:			
Tocilizumab[c]	Adalimumab[c]	1	326
(Patienten, die für eine Weiterbehandlung mit MTX nicht geeignet waren)			
Summe:		35	13 058

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

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

Anzahl relevanter Studien/Patienten: 3

(n= 438)

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

Etanercept

Ergebnisse im Vergleich gegen Placebo sowie:

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

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

und die allgemeine Gesundheit sowie hinsichtlich der Morgensteifigkeit und des körperlichen Funktionsstatus,

- keinen Beleg für einen Zusatznutzen hinsichtlich der Remission und hinsichtlich der strukturellen Gelenkveränderungen (wie Deformitäten, Versteifungen, Kontrakturen), des sozialen Funktionsniveaus und der gesundheitsbezogenen Lebensqualität aufgrund fehlender Daten
- keinen Beleg für einen geringeren oder größeren Schaden durch eine der beiden Prüfinterventionen im Hinblick auf die Gesamt-mortalität und im Hinblick auf schwerwiegende unerwünschte Ereignisse, Studienabbrüche aufgrund von unerwünschten Ereignissen, die Gesamtrate der unerwünschten Ereignisse, schwerwiegende Infektionen und die Gesamtrate der Infektionen.

Für Etanercept gibt es (im Vergleich zu MTX) bei Patienten mit schwerer aktiver und progressiver RA

- einen Anhaltspunkt für einen Zusatznutzen von Etanercept gegenüber MTX hinsichtlich der Remission, hinsichtlich der Symptomatik der RA bezogen auf schmerzhafte Gelenke, geschwollene Gelenke, Schmerz, die globale Einschätzung der Krankheitsaktivität durch den Patienten, die allgemeine Gesundheit sowie die Morgensteifigkeit,
- keinen Beleg für einen Zusatznutzen hinsichtlich der strukturellen Gelenkveränderungen (wie Deformitäten, Versteifungen, Kontrakturen) aufgrund fehlender Daten, hinsichtlich des körperlichen Funktionsstatus, des sozialen Funktionsniveaus und der gesundheitsbezogenen Lebensqualität jeweils aufgrund fehlender Daten
- keinen Beleg für einen geringeren oder größeren Schaden durch eine der beiden Prüfinterventionen im Hinblick auf die Gesamt-mortalität und im Hinblick auf schwerwiegende unerwünschte Ereignisse, Studienabbrüche aufgrund von unerwünschten Ereignissen, die Gesamtrate der unerwünschten Ereignisse, schwerwiegende Infektionen und die Gesamtrate der Infektionen.

Für Tocilizumab im Vergleich zu Adalimumab bei Patienten, die für eine Weiterbehandlung mit MTX nicht geeignet waren, gibt es

- einen Hinweis auf einen Zusatznutzen hinsichtlich der Remission,
- keinen Beleg für einen Zusatznutzen hinsichtlich der Symptomatik der RA bezogen auf schmerzhafte Gelenke, geschwollene Gelenke, Schmerz, die globale Einschätzung der Krankheitsaktivität durch den Patienten und Fatigue, hinsichtlich des körperlichen Funktionsstatus und hinsichtlich der gesundheitsbezogenen Lebensqualität – für strukturelle Gelenkveränderungen (wie Deformitäten, Versteifungen, Kontrakturen) und für das soziale Funktionsniveau lagen keine Daten vor,
- keinen Beleg für einen größeren bzw. geringeren Schaden im Hinblick auf die Gesamtmortalität, schwerwiegende unerwünschte Ereignisse, Studienabbrüche aufgrund von unerwünschten Ereignissen, die Gesamtrate der unerwünschten Ereignisse, schwerwiegende Infektionen und die Gesamtrate der Infektionen.

3.2 Cochrane Reviews

Ruiz Garcia, V. et al., 2017 [24].

Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Fragestellung

To assess the clinical benefits and harms of certolizumab pegol (CZP) in people with RA who have not responded well to conventional disease-modifying anti-rheumatic drugs (DMARDs).

Methodik

Population:

- Adults (18 years and older) with RA who have persistent disease activity.

Intervention:

- Certolizumab pegol (CZP)) at any dose.

Komparator:

- placebo or any DMARD including other biologic agents used to treat RA

Endpunkte:

- proportion of participants 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 (SAEs)
- All withdrawals
- Withdrawals due to adverse events

Recherche/Suchzeitraum:

- Searched in MEDLINE; ; Embase; CINAHL; Cochrane Database of Systematic Reviews (CDSR) and Cochrane Central Register of Controlled Trials (CENTRAL), HTA, DARE, NHS EED (the Cochrane Library); SCOPUS; TOXLINE (TOXNET), ClinicalTrials.gov;the WHO International Clinical Trials Registry Platform (apps.who.int/trialsearch/); clinical trial meta-register database (www.controlled-trials.com/mrct/); reference lists of all identified studies
- Latest update 26 September 2016

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool

Ergebnisse

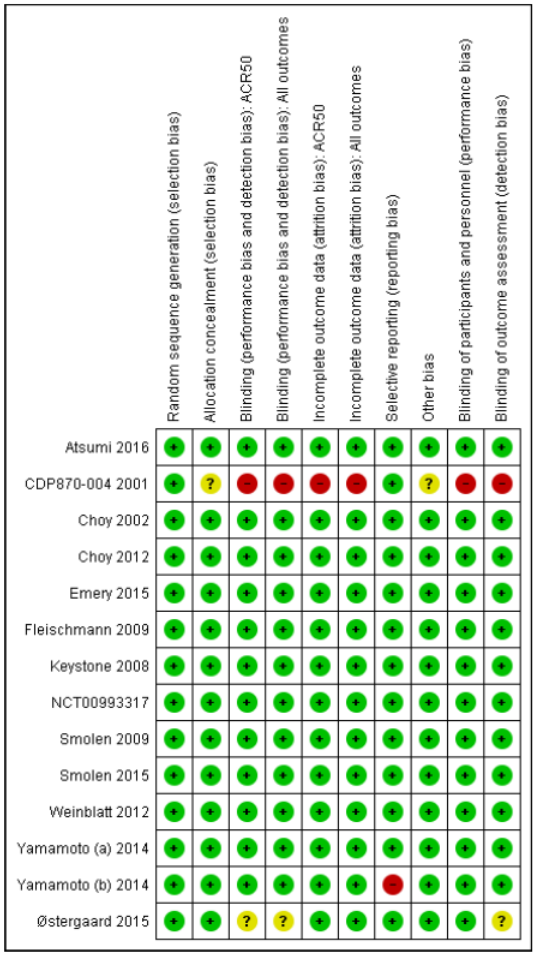
Anzahl eingeschlossener Studien:

- 14 RCTs in total

Qualität der Studien:

- We rated most of the trials at low risk of bias. The overall likelihood of bias seemed to be low.
- All trials funded by UCB, the manufacturer of certolizumab pegol.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Studienergebnisse:

Certolizumab pegol 200 mg sc (with or without MTX) versus placebo (with or without MTX) for rheumatoid arthritis in adults

Patient or population: patients with rheumatoid arthritis in adults
Settings: adults (18 years old or more) who have persistent disease activity
Intervention: certolizumab pegol 200 mg sc (with or without MTX) versus placebo (with or without MTX)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Summary of findings certolizumab pegol 200 mg sc (with or without MTX) versus placebo (with or without MTX)				
ACR 50% improvement Follow-up: mean 24 weeks 200 mg sc certolizumab pegol	**87 per 1000**	**359 per 1000** (328 to 391)	**RR 3.80** (2.42 to 5.95)	1445 (5 studies)	⊕⊕⊕⊕ **high**	Absolute risk difference = 25% (95% CI 20% to 33%). Relative per cent change = 280% (142% to 495%). NNTB = 4 (3 to 5)
HAQ change from baseline Scale from: 0 to 3. Follow-up: mean 24 weeks (lower scores means better function) 200 mg sc certolizumab pegol	The mean HAQ change from baseline in the control groups was **-0.13**	The mean HAQ change from baseline in the intervention groups was **0.35 lower** (0.43 to 0.26 lower)	**MD -0.35** (-0.43 to -0.26)	1268 (4 studies)	⊕⊕⊕○ **moderate**[1]	Absolute risk difference = -12% (95% CI -9% to -14%). Relative per cent change = -21% (-15% to -25%). NNT = 8 (7 to 11)
Proportion of patients achieving DAS < 2.6 (remission) Follow-up: mean 24 weeks 200 mg sc certolizumab pegol	**123 per 1000**	**216 per 1000** (194 to 247)	**RR 2.94** (1.64 to 5.28)	2420 (6 studies)	⊕⊕⊕⊕ **high**	Absolute risk difference = 10% (95% CI 8% to 16%). Relative per cent change = 194% (64% to 428%) NNT = 8 (6 to 12)
Radiological changes: Erosion Scores (ES) Scale from: 0 to 230 Follow-up: 24 weeks 200 mg sc certolizumab pegol	The mean radiological changes: Erosion Scores (ES) in the control groups was **0.7**	The mean Radiological changes: Erosion Scores (ES) in the intervention groups was **0.67 lower** (0.96 to 0.38 lower)	**MD -0.67** (-0.96 to -0.28)	714 (2 studies)	⊕⊕⊕○ **moderate**[1]	Absolute risk difference = -0.29% (95% CI -0.42% to -0.17%). Relative per cent change = -2.90% (-4.16% to -1.65%) NNT = 6 (4 to 10)
Serious adverse events Follow-up: 12 to 24 weeks 200 mg sc certolizumab pegol	**58 per 1000**	**85 per 1000** (59 to 120)	**Peto OR 1.47** (1.13 to 1.91)	3927 (9 studies)	⊕⊕⊕⊕ **high**	Absolute risk difference = 3% (95% CI 1% to 4%). Relative per cent change = 47% (13% to 91%). NNTH = 33 (25 to 100)
All Withdrawals: All doses of certolizumab pegol vs placebo Follow-up: 0 to 52 weeks	**524 per 1000**	**231 per 1000** (203 to 291)	**RR 0.47** (0.39 to 0.56)	5200 (13 studies)	⊕⊕⊕○ **moderate**[2]	Absolute risk difference = -29% (95% CI -16% to -42%). Relative per cent change= -53% (-44% to -61%). NNTH = 3 (2 to 6)
Withdrawals due to adverse events All doses of certolizumab pegol versus placebo Follow-up: 0 to 52 weeks	**38 per 1000**	**52 per 1000** (40 to 73)	**Peto OR 1.45** (1.09 to 1.94)	5236 (12 studies)	⊕⊕⊕⊕ **high**	Absolute risk difference = 2% (95% CI 0% to 3%). Relative per cent change = 45% (9% to 94%). NNTH = 58 (28 to 329)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio; **NNTB:** number needed to treat for an additional beneficial outcome

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]We downgraded the quality of evidence by one level for risk of bias due to attrition bias analysed per protocol. We have rated all the trials at low risk for attrition bias since reasons for attrition/exclusions were reported in most of them, and reasons were similar. However, for HAQ-DI and radiological changes we can only conduct a per protocol analysis, as these are continuous outcomes that count the average number of participants still in the trials. For DAS remission, ACR50, SAEs, all withdrawals and withdrawals due to AEs we conducted an ITT analysis, which is a more conservative approach, not requiring downgrading.
[2]We downgraded the quality of evidence by one level for inconsistency, due to heterogeneity (not all the confidence intervals overlap, and I^2 is 79%).

Anmerkung/Fazit der Autoren

This review confirms that certolizumab pegol compared with placebo is clinically beneficial, improving ACR50, quality of life and increasing the chance of remission. In addition certolizumab pegol compared with placebo reduces the risk of radiographic damage. There is a potential risk of serious adverse events, including hypertension and tuberculosis in susceptible individuals, which should be borne in mind when considering certolizumab pegol. There was no direct evidence comparing certolizumab with other TNF inhibitors.

There is a moderate to high certainty of evidence, obtained from randomised controlled trials, that certolizumab pegol, alone or combined with methotrexate, is beneficial in the treatment of RA. It improved ACR50 (pain, function and other symptoms of RA), health-related quality of life, and the chance of remission of RA, reduced joint damage as seen on the x-ray, but increased serious adverse events. Fewer people stopped taking their treatment, but most of those who did stopped because of serious adverse events. Adverse events were more frequent with active treatment. We found a clinically but not statistically significant risk of serious adverse events.

Singh JA et al., 2017 [26].

Biologics or tofacitinib for people with rheumatoid arthritis unsuccessfully treated with biologics: a systematic review and network meta-analysis

Fragestellung

To compare the benefits and harms of biologics (abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab) and small molecule tofacitinib versus comparator (placebo or methotrexate (MTX)/other DMARDs) in people with RA, previously unsuccessfully treated with biologics.

Methodik

Population:

- Adults 18 years or older, with rheumatoid arthritis (RA) meeting the 1987 American College of Rheumatology (ACR) classification criteria for RA or the 2010 ACR/European League Against Rheumatism (EULAR) classification criteria for RA, , who were biologic-experienced, that is, had been treated unsuccessfully with at least one biologic therapy or tofacitinib.

Intervention:

- Biologics or tofacitinib used alone or in combination with traditional DMARD/other biologic

Komparator:

- placebo alone
- placebo plus traditional DMARDs or biologics
- combinations of DMARDs.

Endpunkte

- ACR50,
- RA disease remission: defined as DAS less than 1.6 or DAS28 less than 2.6

- (modified) Health Assessment Questionnaire ([m]HAQ) score change, proportion achieving minimal clinically important difference on HAQ 0.22 or less
- Radiographic progression: measured by Larsen/Sharp/modified Sharp scores,
- Withdrawals due to adverse events,
- Serious adverse events (SAEs)
- Cancer.

Recherche/Suchzeitraum:

- CENTRAL, MEDLINE, and Embase; and trials registries (WHO trials register, Clinicaltrials.gov in June 2015

Qualitätsbewertung der Studien:

- Cochrane 'Risk of bias' tool & GRADE approach

Ergebnisse

Anzahl/Charakteristika eingeschlossener Studien:

- 12 RCT
- Interventions:
  - 1 trial with tofacitinib
  - 2 trial with tocilizumab
  - 2 trial with rituximab
  - 2 trials with abatacept
  - 1 trial with etanercept
  - 1 trial with certolizumab
  - 1 trial with golilumab
  - 1 trial with etanercept/infliximab
  - 1 trials with abatacept/ etanercept
- Komparatoren:
  - 2 trials with continuation of background DMARD + placebo
  - 1 trial with discontinuation of previously used DMARD + placebo
  - 6 trials with MTX/ DMARD
  - 3 trials with another biologic
- Duration: 8 RCT < 6 months, 2 RCT 6 - 12 months, 2 RCT > 12 months.

Charakteristika der Population:

- 3364 participants included
- Treatment with one or more TNF-biologic had failed, due to inadequate response or intolerance to TNF-biologic in four studies or inadequate response to TNF-biologic only in eight studies

Qualität der Studien:

- Allocation (selection bias):

- 4 of 12 trials (33%) reported adequate sequence generation; 8 (67%) did not describe the method used (unclear risk)
- Allocation concealment as low risk in 4 (33%) trials, unclear in 8 (67%) trials

- Blinding (performance and detection bias)
  - 4 (33%) trials at low risk of performance bias, 6 (50%) at unclear risk of bias, 2 (17%) trials without participant blinding (high risk of performance bias)
  - Low risk of detection bias in 3 (25%) trials, high risk in 2 (17%) and unclear risk in 7 (58%) trials.
- Incomplete outcome data (attrition bias): 3 trials (25%) at low risk of attrition bias; 1 trial (8%) at unclear risk, 8 (67%) trials were at high risk of attrition bias
- Selective reporting (reporting bias): 1 (8%) trial at low risk of bias, 11 (92%) trials as unclear risk (no study protocols available)
- Other potential sources of bias: 12 (100%) trials at low risk of bias resulting from major baseline imbalance

Studienergebnisse:

HAQ:

- Results from standard MA:
  - 2 studies with 981 participants
  - Statistically significant and potentially clinically meaningful change for biologic with concomitant MTX compared to MTX/DMARD: mean difference in HAQ improvement of -0.29 (95% CI -0.36 to -0.21), I^2 = 0%.
  - a “negative” sign indicates improvement in function; lower values indicate better function

Compari-son		No. of par-ticipants (studies)	Direct evidence		
				Absolute risk differ-ence, NNTB	Quality of evidence

Outcome: Health Assessment Questionnaire (HAQ) score, 0-3 (higher = worse; A "negative sign" indicates improvement) : A measure of function			**MD (95% CI)**		
All biologics	vs. placebo	n/a			
All biologics + MTX	vs. MTX/ DMARD	959 (2 studies)	-0.29 (-0.36 to -0.21)	-9.7% (-12% to -7.0%) , NNTB = 5 (4 to 7)	⊕⊕⊕⊕ high[b]
TNF biologic + MTX	vs. MTX/ DMARD	461 (1 study)	-0.25 (-0.40 to -0.10)	-8.3% (-13% to -3%) , NNTB = 5 (7 to 16)	⊕⊕⊕⊕ high[b]
Non-TNF biologic + MTX	vs. MTX/ DMARD	498 (1 study)	-0.37 (-0.46 to -0.28)	-12.3% (-15% to -9%) , NNTB = 4 (3 to 5)	⊕⊕⊕⊕ high[b]
Tofacitinib + MTX	vs. MTX/ DMARD	399 (1 study)	-0.27 (-0.39 to -0.14)	-9% (-13% to -4.7%) , NNTB = 5 (4 to 10)	⊕⊕⊕⊕ high[b]

Remission (defined as DAS less than 1.6 or DAS28 less than 2.6)

- 2 studies with 959 participants
- Results from standard MA:
  - Biologic + MTX vs. MTX/DMARD associated with a statistically higher odd of remission, OR 23.07 (95% CI 4.53 to 117.40), I^2 = 0%

Comparison		**No. of participants (studies)**	**Direct evidence**		
				Absolute risk difference, NNTB	**Quality of evidence**

Outcome: Remission (defined as DAS <1.6 or DAS28 <2.6)			**RR (95% CI)**		
All biologics	vs. placebo	389 (1 study)	13.51 (1.85 to 98.45)	9% (5% to 13%), NNTB = 11 (3 to 136)	⊕⊕⊕○ moderate (downgraded for imprecision)[d]
All biologics + MTX	vs. MTX/DMARD	959 (2 studies)	20.73 (4.13 to 104.16)	10% (8% to 13%), NNTB = 17 (4 to 96)	⊕⊕⊕○ moderate (downgraded for imprecision)[d]
TNF biologic + MTX	vs. MTX/DMARD	461 (1 study)	16.21 (2.24 to 117.51)	10% (6% to 13%), NNTB = 11 (3 to 110)	⊕⊕⊕○ moderate (downgraded for imprecision)[d]
Non-TNF biologic + MTX	vs. MTX/DMARD	498 (1 study)	33.72 (2.08 to 546.23)	10% (7% to 14%), NNTB = n/a[e]	⊕⊕⊕○ moderate (downgraded for imprecision)[d]
Tofacitinib + MTX	vs. MTX/DMARD	398 (1 study)	15.44 (0.93 to 256.10)	6% (3% to 9%), NNTB = n/a[e]	⊕⊕⊕○ moderate (downgraded for imprecision)[d]

Withdrawals due to adverse events

- 2 studies with 611 participants
- Results from standard MA:
  - Biologic + MTX vs. MTX/DMARD not associated with a statistically significant higher odds, OR 3.42 (95% CI 0.87 to 13.54), I^2 = 0%

Comparison		No. of participants (studies)	Direct evidence		
				Absolute risk difference, NNTB	Quality of evidence
Outcome: Withdrawals due to adverse events			**RR (95% CI)**		
All biologics	vs. placebo	428 (2 studies)	0.62 (0.13 to 2.93)	-1% (-4% to 3%), NNTB = n/a	⊕⊕◌◌ low (downgraded for serious imprecision)[a,e]
All biologics + MTX	vs. MTX/DMARD	611 (2 studies)	3.32 (0.86 to 12.85)	5% (-3% to 13%), NNTB = n/a	⊕⊕◌◌ low (downgraded for serious imprecision)[a,e]
TNF biologic + MTX	vs. MTX/DMARD	n/a			
Non-TNF biologic + MTX	vs. MTX/DMARD	611 (2 studies)	3.32 (0.86 to 12.85)	5% (-4% to 13%), NNTB = n/a	⊕◌◌◌ very low (downgraded for serious imprecision/ inconsistency)[a,d,f]
Tofacitinib + MTX	vs. MTX/DMARD	399 (1 study)	0.99 (0.41 to 2.39)	0% (-5% to 5%), NNTB = n/a	⊕⊕◌◌ low (downgraded for serious imprecision)[a,d]

Serious adverse events

- 3 studies with 1,072 participants
- Results from standard MA:
  - Biologic + MTX vs. MTX/DMARD not associated with a statistically significant higher odds, OR 0.67 (95% CI 0.41 to 1.09), I^2 = 0%

Comparison		No. of participants (studies)	Direct evidence		
				Absolute risk difference, NNTB	Quality of evidence
Outcome: Serious adverse events			RR (95% CI)		
All biologics	vs. placebo	428 (2 studies)	0.93 (0.51 to 1.68)	-1% (-7% to 5%), NNTB = n/a	⊕⊕◌◌ low (downgraded for serious imprecision)[a,d]
All biologics + MTX	vs. MTX/DMARD	1072 (3 studies)	0.69 (0.44 to 1.09)	-2% (-5% to 1%), NNTB = n/a	⊕⊕⊕◌ moderate (downgraded for imprecision)[a]
TNF biologic + MTX	vs. MTX/DMARD	461 (1 study)	0.55 (0.25 to 1.22)	-3% (-8% to 1%), NNTB = n/a	⊕⊕◌◌ low (downgraded for serious imprecision)[a,d]
Non-TNF biologic + MTX	vs. MTX/DMARD	611 (2 studies)	0.77 (0.45 to 1.33)	-1% (-6% to 3%), NNTB = n/a	⊕⊕◌◌ low (downgraded for serious imprecision)[a,d]
Tofacitinib + MTX	vs. MTX/DMARD	399 (1 study)	0.33 (0.09 to 1.15)	-3% (-7% to 1%), NNTB = n/a	⊕⊕◌◌ low (downgraded for serious imprecision)[a,d]

Cancer

- 1 study with unknown number of participants
- Compared to MTX/DMARD, biologic with concomitant MTX was not associated with a statistically significant higher odds of cancer, OR 4.53 (95% CI 0.07 to 285.5);

Comparison		No. of participants (studies)	Direct evidence		
				Absolute risk difference, NNTB	Quality of evidence
Outcome: Cancer (note: Peto OR used but			RR (95% CI)		
can interpret as RR due to low event rate)					
All biologics	vs. placebo	n/a			
All biologics + MTX	vs. MTX/DMARD	550 (2 studies)	4.54 (0.24 to 85.36)	1% (-1% to 2%), NNTB = n/a	⊕⊕◌◌ low (downgraded for serious imprecision)[a,d]
TNF biologic + MTX	vs. MTX/DMARD	459 (1 study)	4.54 (0.24 to 85.36)	1% (-1% to 2%), NNTB = n/a	⊕⊕◌◌ low (downgraded for serious imprecision)[a,d]
Non-TNF biologic + MTX	vs. MTX/DMARD	91 (1 study)	Not estimable	0% (-5% to 5%), NNTB = n/a	⊕⊕◌◌ low (downgraded for serious imprecision)[a,d]
Tofacitinib + MTX	vs. MTX/DMARD	n/a			

Anmerkung/Fazit der Autoren

Implications for practice

Due to limited direct head-to-head comparator trial data for biologics in people with rheumatoid arthritis (RA) whose treatment with a biologic has failed, practitioners are faced with a dilemma in how to choose the next biologic or tofacitinib. This review provides a summary of comparisons of biologics or tofacitinib […] in combination with methotrexate (MTX) or disease-modifying anti-rheumatic drugs (DMARDs) to MTX/DMARD, in people with RA whose treatment with a biologic has failed. We found moderate- to high-quality evidence that […] biologic +MTX (versus MTX/DMARD) were generally efficacious, with inconclusive evidence regarding harms. Specifically, results were inconclusive for withdrawals due to adverse events, serious adverse events and cancer with […] biologic + MTX therapy compared to MTX/DMARD in standard meta-analyses and NMA, with wide confidence intervals encompassing the null effect and a potentially important increase in each harm. This indicates that more studies are needed for a more confident assessment of relative harms. Overall, our review provides support for the use of a second biologic in people previously unsuccessfully treated with a biologic. Only one study provided data on tofacitinib, which limits our confidence in this finding.

Kommentare zum Review

No restriction on degree of severity of RA.

Network diagram shown for ACR50 only. Results from NMA therefore not reported. Integration of multi-arm studies generally unclear.

Radiographic endpoints and ACR 50 not reported.

Singh JA et al., 2016 [27].

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)

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.

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:

- Biologics (abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab) or Tofacitinib, used as monotherapy (without MTX and other traditional DMARDs)

Komparator:

- placebo alone
- placebo plus traditional DMARDs (including methotrexate (MTX)
- biologics
- combinations of DMARDs.

Endpunkte

- ACR50,
- RA disease remission: defined as DAS less than 1.6 or DAS28 less than 2.6
- (modified) Health Assessment Questionnaire ([m]HAQ) score change, proportion achieving minimal clinically important difference on HAQ 0.22 or less
- Radiographic progression: measured by Larsen/Sharp/modified Sharp scores,
- Withdrawals due to adverse events,
- Serious adverse events (SAEs)

- Cancer.

Recherche/Suchzeitraum:

- The Cochrane Central Register of Controlled Trials (CENTRAL; The Cochrane Library 2015, Issue 6), MEDLINE (via OVID1946 to June 2015), and Embase (via OVID1947 to June 2015)

Qualitätsbewertung der Studien:

- Cochrane 'Risk of bias' tool & GRADE approach

Ergebnisse

Number/characteristics of studies:

- Update includes 40 new RCTs for a total of 46 RCTs, of which 41 studies with 14 049 participants provided data
- Intervention: no distribution reported
- Komparator:
  - 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)
- Duration: 27 trials (66%) < 6 months, 8 trails (19%) 6 - 12 months, 6 trials (15%) > 12 months

Qualität der Studien:

- 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

Studienergebnisse:

HAQ:

- Results from standard meta-analysis (MA):
  - 6 studies with 1,831 participants
  - Biologic monotherapy associated with statistically significant improvement in HAQ scores versus MTX/other DMARDs, with a MD of -0.27 (95% CI, -0.40 to -0.14), **I^2 = 91% (P<0.00001)**

Remission (defined as DAS less than 1.6 or DAS28 less than 2.6):

- Results from standard meta-analysis (MA):
  - 4 studies with 1,204 participants
  - Biologic monotherapy not associated with statistically significant higher OR of remission, OR 1.65 (95%CI, 0.98 to 2.80), I^2=42% (P = 0,16)

Withdrawals due to adverse events

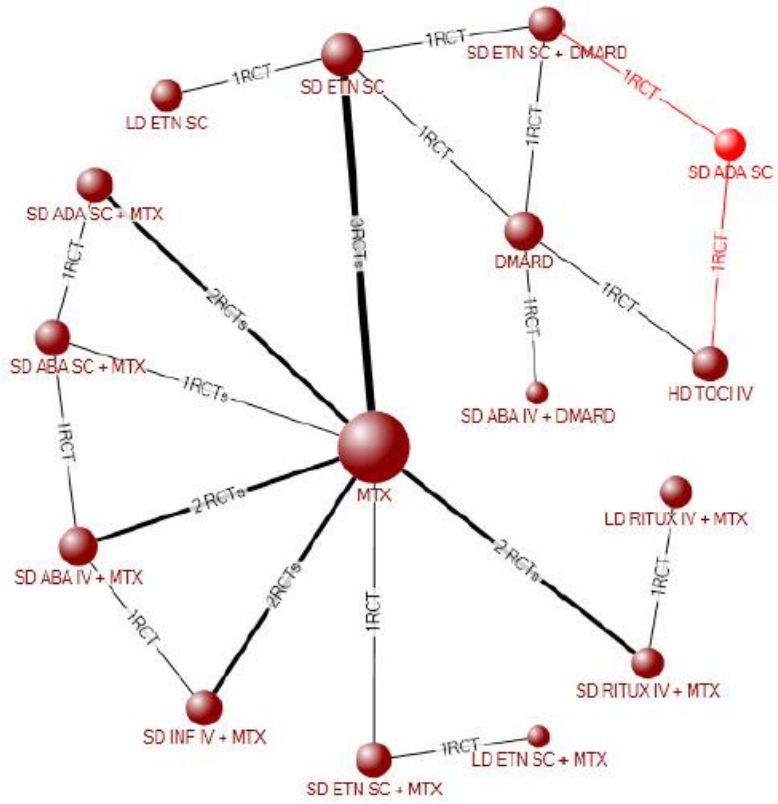
- Results from standard MA:
  - 9 studies with 3,218 participants
  - Biologic monotherapy associated with no statistically significant increase in the likelihood of withdrawals due to AEs versus MTX/other DMARDs with an OR of 1.09 (95% CI, 0.67 to 1.79), **I^2 = 62% (P=0,006)**

Serious adverse events

- Results from standard MA:
  - 7 studies with 2,313 participants
  - biologic monotherapy not associated with statistically significantly higher OR of SAEs versus MTX/other DMARDs, 1.54 (95% CI, 0.94 to 2.51), I^2 = 30% (P=0,2)

Cancer

- Results from standard MA:
  - 6 studies with 2,664 participants
  - biologic monotherapy associated with no statistically significant increase in odds of cancer versus MTX/DMARD, Peto's OR 1.40 (95% CI, 0.67 to 2.93), I^2 = 18% (P=0,3)
- Results from NMA:
  - Network with 24 studies with 10,843 participants, 7 studies had at least one arm with biologic monotherapy



Network diagram for cancer: biologic monotherapy

- The overall odds (95% CrI) of cancer by the type of medication, and type of biologic versus MTX/DMARD were as follows:

  1. Type of medication

     i) Compared to TNF inhibitors, the OR of cancer with non-TNF biologic were not statistically significantly different at 0.95 (95% CrI, 0.22 to 4.35).

  2. Type of biologic: receptor versus antibody

     i) Compared to etanercept monotherapy, neither monoclonal TNF antibody monotherapy nor non-TNF biologic monotherapy, were associated with any significant differences in the odds of cancer, OR 0.91 (95% CrI, 0.06 to 13.28) and 0.91 (95% CrI, 0.17 to 5.40), respectively.

Anmerkung/Fazit der Autoren

Implications for practice

[…]

Biologic monotherapy improved RA signs and symptoms (ACR50), physical function […] compared to active comparator (MTX/other DMARDs). There were no significant differences in RA remission. We noted inconclusive results for withdrawals due to adverse events, serious adverse events and cancer with biologic monotherapy versus active comparator, with wide confidence intervals.

[…]

Kommentare zum Review

No restriction on degree of severity of RA.

Network diagram shown for cancer only. Results from NMA for all other EP therefore not reported. Integration of multi-arm studies generally unclear.

Radiographic endpoints and ACR 50 not reported.

Singh JA et al., 2016 [25].

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 (Review)

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).

Methodik

Population:

- Adults, 18 years or older, with RA meeting the 1987 American College of Rheumatology (ACR) classification criteria for RA or the 2010 ACR/European League Against Rheumatism (EULAR) classification criteria for RA and who were MTX/DMARD-experienced (including MTX/DMARDIR).

Intervention:

- Biologics (abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab) or tofacitinib used alone or in combination with traditional DMARD/ other biologics

Komparator:

- placebo (PL) alone
- placebo plus traditional DMARDs (including methotrexate (MTX)
- biologics
- combinations of DMARDs.

Endpunkte

- ACR50,
- RA disease remission: defined as DAS less than 1.6 or DAS28 less than 2.6
- (modified) Health Assessment Questionnaire ([m]HAQ) score change, proportion achieving minimal clinically important difference on HAQ 0.22 or less
- Radiographic progression: measured by Larsen/Sharp/modified Sharp scores,
- Withdrawals due to adverse events,

- Serious adverse events (SAEs)
- Cancer.

Recherche/Suchzeitraum:

- The Cochrane Central Register of Controlled Trials (CENTRAL; The Cochrane Library 2015, Issue 6), MEDLINE (via OVID1946 to June 2015), and Embase (via OVID 1947 to June 2015)

Qualitätsbewertung der Studien:

- Cochrane 'Risk of bias' tool & GRADE approach

Ergebnisse

Number/characteristics of studies:

- Update includes 90 RCTs; 79 RCTs with 32,874 participants provided usable data
- Intervention: no distribution reported
- Comparator: no distribution reported
- Duration: 87% of trials ≤ 12 months, 13% > 12 months

Qualität der Studien:

- Few trials were at high risk of bias for blinding of assessors/participants (13% to 21%), selective reporting (4%) or major baseline imbalance (8%); a large number had unclear risk of bias for random sequence generation (68%) or allocation concealment (74%)

Studienergebnisse:

HAQ:

- Results from standard meta-analysis (MA):
  - 29 studies with 10,403 participants
  - Biologic therapy associated with statistically significant improvement in HAQ scores vs. comparator (MTX/DMARD/PL), in patients taking biologic with concomitant MTX/DMARD with a mean difference (MD) of -0.25 (95% CI -0.28 to -0.22), **I^2 = 95% (P<0.00001)**

Remission (defined as DAS less than 1.6 or DAS28 less than 2.6):

- Results from standard meta-analysis (MA):
  - 21 studies with 8,691 participants
  - Participants receiving biologic +MTX/DMARD had higher odds of remission vs. comparator (MTX/DMARD/PL) with an OR of 3.81 (95%CI, 2.90 to 5.00); **I^2 = 60% (P=0.0002)**

Withdrawals due to adverse events

- Results from standard MA:
  - 42 studies with 16,756 participants

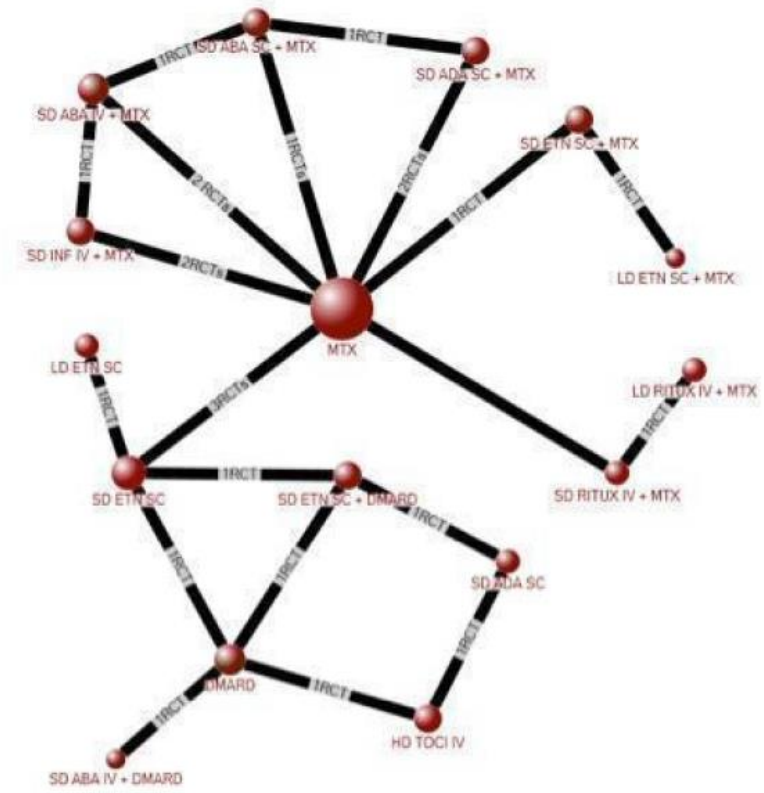
- Biologic therapy associated with no statistically significant increase in the likelihood of withdrawals due to adverse events, vs. comparator (MTX/DMARD/PL), OR of 1.14 (95% CI, 0.97 to 1.35), I^2 = 0%

Serious adverse events

- Results from standard MA:
  - 39 studies with 17,499 participants
  - Biologic therapy not associated with statistically significant increase in odds of SAEs versus comparator (MTX/DMARD/PL), Peto OR 1.12 (95% CI 0.99 to 1.27), I^2 = 12% (P=0,26)

Cancer

- Results from standard MA:
  - 15 studies with 5,661 participants
  - Biologic therapy is inconclusive in the risk of cancer due to few events and resulting wide confidence intervals, compared to comparator (MTX/DMARD/PL), Peto OR of 1.07 (95% CI 0.68 to 1.68); I^2 = 0%
- Results from NMA:
  - Network with 24 studies with 10,843 participants, 19 studies included at least one arm with participants on a biologic with concomitant MTX/other DMARDs (most often MTX)



Network diagram for cancer

- The overall odds (95% CrI) of cancer by the type of biologic:

1. Type of biologic (23 studies, 9,386 participants)

   i) Participants receiving MTX/DMARD, compared to TNF inhibitors, the odds of cancer with non-TNF biologic were no different, Peto OR was 0.83 (95% CrI 0.38 to 1.71).

2. Type of biologic: receptor versus antibody (23 studies, 9,386 participants)

   i) In participants receiving MTX, compared to non-TNF biologic, neither etanercept nor monoclonal TNF antibodies, were associated with any significant differences in the odds of cancer, Peto OR 1.54 (95% CrI 0.56 to 4.51) and 1.00 (95% CrI 0.38 to 2.62), respectively.

Anmerkung/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.

Kommentare zum Review

No restriction on degree of severity of RA.

No separate analyses by active comparator and placebo.

Network diagram shown for cancer only. Results from NMA for all other EP therefore not reported. Integration of multi-arm studies generally unclear.

All MA with random effects model (except MA on SAE & cancer), regardless of statistical heterogeneity.

Radiographic endpoints and ACR 50 not reported.

Hazlewood GS et al., 2016 [15].

Methotrexate monotherapy and methotrexate combination therapy with traditional and biologic disease modifying anti-rheumatic drugs for rheumatoid arthritis: A network meta-analysis

Fragestellung

To compare methotrexate and methotrexate-based DMARD combinations for rheumatoid arthritis in patients naïve to or with an inadequate response (IR) to methotrexate.

Methodik

Population:

- Adults (age > 18 years) with RA, according to 1958, 1987 or 2010 classification criteria

Intervention:

- Oral methotrexate monotherapy
- Parenteral methotrexate monotherapy (subcutaneous or intra-muscular)

- Methotrexate combined with conventional synthetic DMARDs. Conventional synthetic DMARDs were limited to: anti-malarials (hydroxychloroquine/chloroquine), sulfasalazine, leflunomide, cyclosporine, intra-muscular gold and azathioprine.
- Methotrexate combined with biologic DMARDs, including anti-TNF inhibitors (adalimumab, certolizumab, etanercept, golimumab, infliximab), abatacept, rituximab, and tocilizumab.
- Methotrexate combined with tofacitinib

Komparator:

- Not specified.

Endpunkte

- Major outcomes (ACR50 response, radiographic progression and withdrawals due to adverse events)
- Multiple minor outcomes

Recherche/Suchzeitraum:

- MEDLINE, EMBASE and CENTRAL from inception to January 19, 2016.

Qualitätsbewertung der Studien:

Cochrane 'Risk of bias' tool & GRADE approach

Ergebnisse

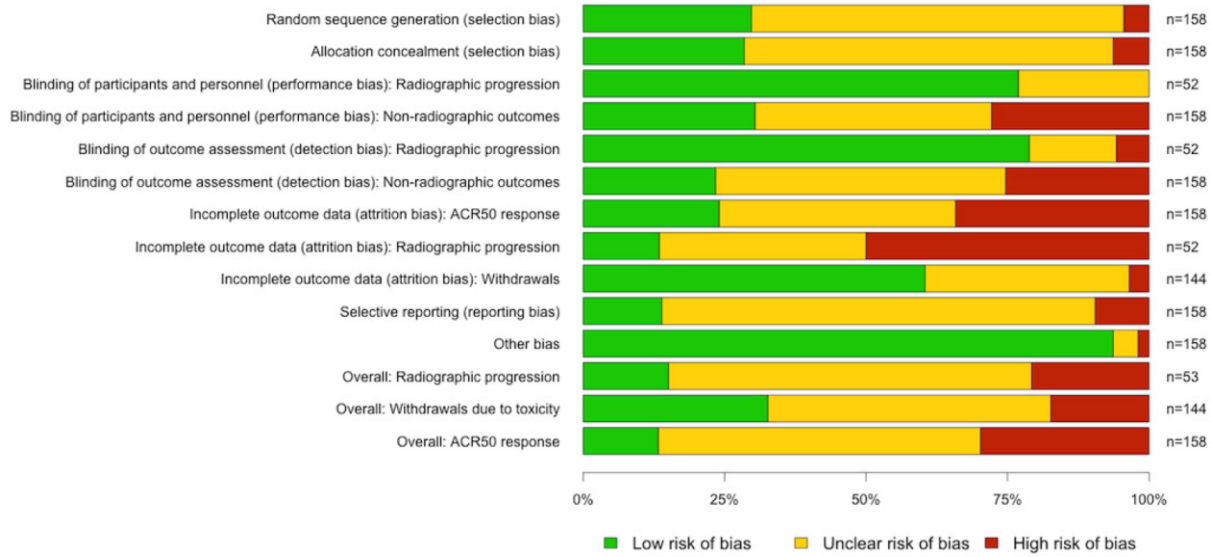
Number/characteristics of studies:

- 158 trials included over 37,000 patients
- Interventions:
  - 80 (51%) compared methotrexate + biologic DMARDs or tofacitinib to methotrexate monotherapy or made comparisons of different dosing formulations (subcutaneous or intravenous) of the same biologic DMARD
  - 8 'comparative effectiveness' trials, with four providing head-to-head comparisons of different biologic DMARDs/tofacitinib and four comparing methotrexate + biologic DMARDs to methotrexate + conventional synthetic DMARD therapy
  - Trials ranged in duration from 12 to 104 weeks

Charakteristika der Population:

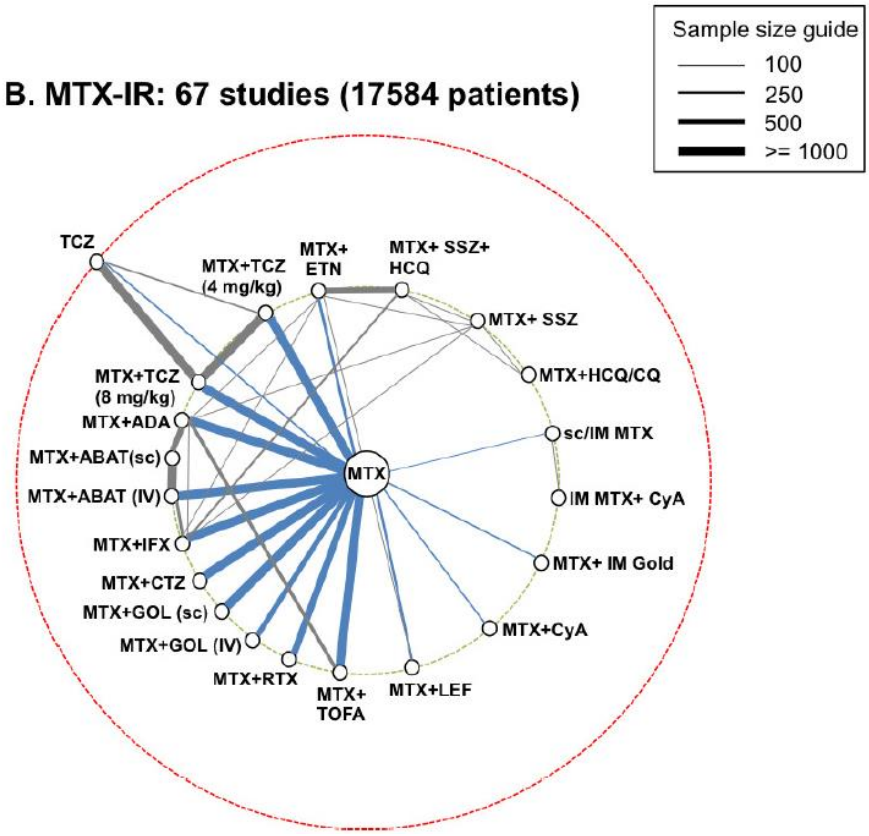
- Median baseline swollen joint count across the trials was high at 15, with a similar distribution across medication classes.

Qualität der Studien:



Methodological quality of included reviews

Studienergebnis:



Networks of included studies for methotrexate-inadequate response populations (B). Each line represents a direct comparison between two treatments from one or more trials. The line thickness is directly proportional to the total sample size of all trials for that comparison (line length has no meaning). Biologic/targeted synthetic DMARDs are shown on the left of each network and conventional synthetic DMARDs on the right. Treatments on the innermost circle (green hashed line) are treatments of interest, whereas treatments on the outermost circle (red

hashed line) are other treatments that form links between treatments of interest. Comparisons to methotrexate are shown in blue. Two trials were included in both analyses.

Withdrawals due to adverse events

- 53 trials with a total follow-up of 9950 patient-years included
- Methotrexate plus ciclosporin and methotrexate plus tocilizumab 8 mg/kg were the only treatments with statistically significant higher rates of withdrawals due to adverse events relative to oral methotrexate (RR = 3.27 [95 CI; 1.20 to 9.57]); Low (indirectness, imprecision)
- In pair wise comparisons, MTX plus subcutaneous abatacept and methotrexate plus intravenous abatacept were associated with a statistically significant lower rate of withdrawals due to adverse events than several treatments, including methotrexate plus biologic DMARDs and triple therapy.

Table C14. Treatment rankings for withdrawals due to adverse events: MTX-inadequate response

Intervention	Probability that treatment is best (%)	Average ranking (1=best, 17=worst) median (95%CrI)
MTX+ABAT (sc)	64.75	1 (1 to 5)
MTX+GOL (sc)	10.53	5 (1 to 15)
MTX+GOL (IV)	9.03	8 (1 to 17)
MTX+ABAT (IV)	6.85	3 (1 to 7)
MTX+ETN	3.18	7 (1 to 15)
MTX+IMGold	2.87	16 (1 to 17)
MTX+RTX	0.77	13 (3 to 17)
MTX+LEF	0.61	12 (3 to 17)
MTX+TOFA	0.43	7 (2 to 15)
MTX+CTZ	0.38	9 (3 to 16)
MTX	0.28	5 (2 to 8)
MTX+SSZ+HCQ	0.18	12 (4 to 17)
MTX+TCZ (4 mg/kg)	0.06	11 (4 to 16)
MTX+CyA	0.04	16 (7 to 17)
MTX+TCZ (8 mg/kg)	0.03	11 (5 to 16)
MTX+IFX	0.01	11 (5 to 15)
MTX+ADA	0	9 (4 to 15)

Anmerkung/Fazit der Autoren

Implications for practice

On the basis of all available direct and indirect evidence, our results suggest that triple therapy (methotrexate + sulfasalazine + hydroxychloroquine) is effective in […] methotrexate inadequate response patients and not statistically different from methotrexate plus biologic therapy for controlling disease activity. Other conventional synthetic DMARD combinations, including methotrexate + hydroxychloroquine, methotrexate + leflunomide and the less commonly used methotrexate + intra-muscular gold were superior to oral methotrexate after an inadequate response to methotrexate, although the quality of evidence or magnitude of effect was lower than for methotrexate + sulfasalazine + hydroxychloroquine. […] For most

treatments, withdrawals due to adverse events were similar and not statistically different from oral methotrexate. Given these findings and cost considerations, it would be difficult to justify the use of methotrexate + biologic DMARDs prior to an adequate trial of combination therapy with methotrexate + conventional synthetic DMARDs (preferably methotrexate + sulfasalazine + hydroxychloroquine).

Kommentare zum Review

No restriction on degree of severity of RA.

Only results for the subgroup "Methotrexate-inadequate patients" presented.

Integration of multi-arm studies in NMA unclear.

Results from standard MA presented as League-Tables.

Radiographic endpoints not reported.

3.3 Systematische Reviews

Bae S-C et al., 2018 [2].

Comparison of the efficacy and safety of tofacitinib and baricitinib in patients with active rheumatoid arthritis: a Bayesian network meta-analysis of randomized controlled trials

Fragestellung

The present study aimed to use a network meta-analysis to investigate the relative efficacy and safety of tofacitinib and baricitinib in patients with active RA and an inadequate response to disease-modifying anti-rheumatic drugs (DMARDs) or biologics.

Methodik

Population:

- Active RA that responded inadequately to DMARDs or biologics

Intervention:

- Tofacitinib or baricitinib in combination with DMARDs including MTX

Komparator:

- Placebo in combination with DMARDs including MTX

Endpunkte (e.g. primary/secondary outcomes):

- Efficacy outcome: ACR 20% improvement (achieved an ACR20 response)
- Safety outcome: number of patients who experienced serious adverse events (SAEs)

Recherche/Suchzeitraum:

- MEDLINE, EMBASE, the Cochrane Controlled Trials Register, and the American College of Rheumatology (ACR) and European League against Rheumatism (EULAR) conference proceedings up to April 2018

Qualitätsbewertung der Studien:

- Jadad

Ergebnisse

Anzahl/Charakteristika eingeschlossener Studien:

- 12 RCT with 5883 patients (2964 events for efficacy and 206 events for safety)
- Follow-up duration 6 months in 2 RCT, 3 month in 10 RCT

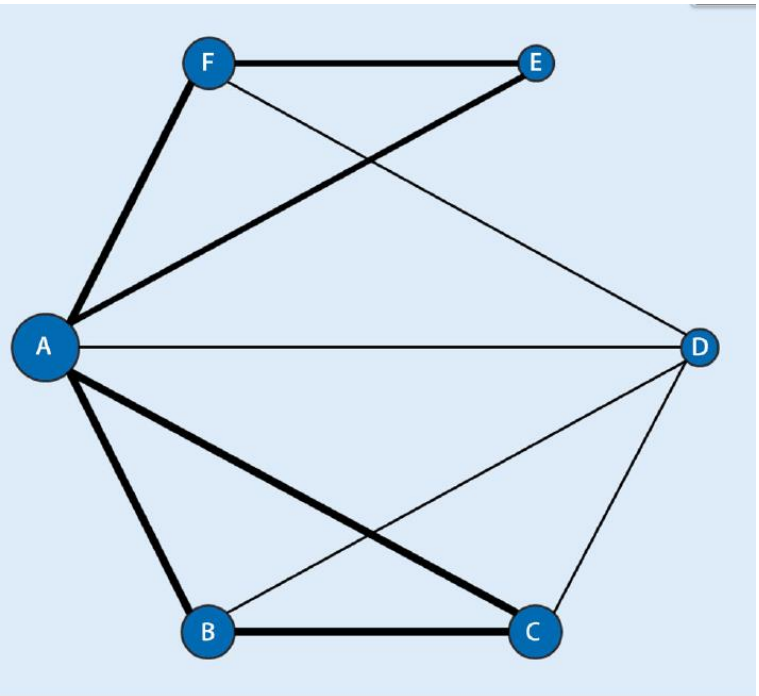
Charakteristika der Population:

- 3 RCT with DMARD- incomplete response (IR) patients (N=1541)
- 7 RCT with MTX-IR patients (N=3416)
- 1 RCT with TNF-IR patients (N=399)
- 1 RCT with Biologic-IR patients (N=527)

Qualität der Studien:

- Jadad scores between 3 - 5 (Median: 3,5)

Studienergebnisse:



Evidence network diagram of networkmeta-analysis comparisons.The width of each edge is proportional to the number of randomized controlled trials comparing each pair of treatments, and the size of each treatment node is proportional to the number of randomized participants (sample size). A: Placebo+MTX, B: Tofacitinib 5mg+MTX, C: Tofacitinib 10mg+MTX, D: Adalimumab+MTX, E: Baricitinib 2mg+MTX, F Baricitinib 4mg+MTX

- Results of the random- and fixed effects models yielded the same interpretation, indicating that the results of this network meta-analysis were robust
- Inconsistency plots assessing network inconsistencies between direct and indirect estimates showed a low possibility of inconsistencies that might significantly affect the results of the network meta-analysis

Safety (SAE)

Adalimumab+MTX					
0.82 (0.25 – 2.50)	Baricitinib 2 mg+MTX				
0.54 (0.22 – 1.31)	0.66 (0.31 – 1.54)	Placebo+MTX			
0.56 (0.21 – 1.50)	0.67 (0.31 – 1.59)	1.03 (0.55 – 1.86)	Baricitinib 4 mg+MTX		
0.40 (0.16 – 1.04)	0.49 (0.18 – 1.38)	0.74 (0.39 – 1.42)	0.71 (0.30 – 1.84)	Tofacitinib 10 mg+MTX	
0.39 (0.15 – 1.01)	0.48 (0.17 – 1.34)	0.72 (0.38 – 1.35)	0.70 (0.30 – 1.72)	0.98 (0.56 – 1.71)	Tofacitinib 5 mg+MTX

b

League tables showing the results of the network meta-analysis comparing the effects of all drugs including odds ratios and 95% credible intervals. b Tolerability: Odds ratio <1 indicates that the top-left treatment is better

- Ranking probability based on SUCRA values indicated that adalimumab+MTX, baricitinib 2mg+MTX, and placebo+MTX had a higher probability of being the safest treatment (SUCRA= 0.877, 0.782, 0.475, respectively), followed by baricitinib 4mg+MTX (SUCRA= 0.474), tofacitinib 10mg+MTX (SUCRA= 0.208), and tofacitinib 5mg+MTX (SUCRA=0.184)

Anmerkung/Fazit der Autoren

In conclusion, we conducted a Bayesian network meta-analysis involving12 RCTs and found that tofacitinib 10mg+MTX and baricitinib 4mg+MTX were the most efficacious interventions for RA patients with an inadequate response to DMARD or biologics therapy and that neither was associated with a significant risk of SAEs. Long-term studies are warranted to determine the relative efficacy and safety of tofacitinib and baricitinib in a large number of patients with active RA that is inadequately responsive to MTX or biologics.

Kommentare zum Review

No restriction on degree of severity of RA.

Results on ACR20 not extracted.

Integration of multi-arm studies in NMA unclear.

Short follow-up (3 month) in 10/12 RCT.

Bae S-C et al., 2018 [1].

Comparative efficacy and safety of TNF-inhibitor plus methotrexate versus oral triple therapy in patients with active rheumatoid arthritis inadequately responding to methotrexate: A meta-analysis of randomized controlled trials

Fragestellung

The study aimed to assess the efficacy and safety of tumor necrosis factor inhibitor (TNFI) with methotrexate (MTX) vs. oral triple therapy in patients with active rheumatoid arthritis (RA), showing inadequate response to MTX.

Methodik

Population:

- Patients with active RA who exhibited an inadequate response to MTX

Intervention:

- TNFI+MTX

Komparator:

- triple therapy (combination of MTX, sulfasalazine (SSZ), and hydroxychloroquine (HCQ),)

Endpunkte (e.g. primary/secondary outcomes):

- Efficacy outcome: ACR20, ACR50, and ACR70 response rate, change in total Sharp score
- Safety outcome: incidence of infection, number of serious adverse events (AEs), and number of patients withdrawn due to AEs

Recherche/Suchzeitraum:

- PubMed, Embase, and the Cochrane Controlled Trials Register to identify available articles (up to June 2017)

Qualitätsbewertung der Studien:

- Jadad

Ergebnisse

Anzahl/Charakteristika eingeschlossener Studien:

- 3 RCT with 990 patients (2964 events for efficacy and 206 events for safety)
- Follow-up periods ranged from 24 to 104 weeks

Charakteristika der Population:

- 558 patients randomized to TNFI+MTX,
- 432 patients randomized to triple therapy

Qualität der Studien:

- Jadad scores between 3 - 5

Studienergebnisse:

- With respect to the number of patients who experienced at least one serious adverse event, there was no significant difference between the TNFI+MTX group and the triple therapy group (RR 1.033, 95% CI 0.710 – 1.504, p = 0.864)
- Withdrawal due to AEs did not differ between the TNFI+MTX group and the triple therapy group (RR 0.736, 95% CI 0.431 – 1,257, p = 0.261)
- TNFI+MTX resulted in more infections than did triple therapy (RR 1.513, 95% CI 1.149 – 1.992, p = 0.003, I^2 = 0%)

Anmerkung/Fazit der Autoren

[…] However, we also found that TNFI+MTX was associated with a higher risk of infection. Our results suggest a difference in efficacy and safety between TNFI+MTX and triple therapy

in patients with active RA refractory to MTX therapy. Long-term studies are needed to determine the relative efficacy and safety of TNFI+MTX and triple therapy in a large number of patients with active RA who inadequately respond to MTX.

Kommentare zum Review

No restriction on degree of severity of RA.

Weights assigned in MA (fixed effect model) not presented.

Unclear how different follow-up durations (24 weeks, 48-102 weeks, 104 weeks) were taken into account.

Radiographic endpoints and ACR response not reported.

Bae S-C et al., 2018 [3].

Comparison of the efficacy and tolerability of tocilizumab, sarilumab, and sirukumab in patients with active rheumatoid arthritis: a Bayesian network meta-analysis of randomized controlled trials

Fragestellung

To compare the efficacy and tolerability of tocilizumab, sarilumab, and sirukumab in patients with active RA and an inadequate response to MTX or TNF inhibitors

Methodik

Population:

- active RA that inadequately responded to TNF inhibitors or DMARDs including MTX

Intervention:

- tocilizumab, sarilumab, or sirukumab,with or without DMARDs including MTX

Komparator:

- placebo + DMARDs including MTX

Endpunkte:

- outcomes of efficacy and tolerability at 24 wk

Recherche/Suchzeitraum:

- databases of MEDLINE, EMBASE, and Cochrane Controlled Trials Register for entries up to December 2017

Qualitätsbewertung der Studien:

- Jadad

Ergebnisse

Anzahl eingeschlossener Studien:

- 14 RCTs, which included 9753 patients (2596 efficacy-related events and 776 safety-related events),

Qualität der Studien:

- Jadad scores of the studies were between 3 and 5, which were indicative of high-quality studies

Studienergebnisse:

- number of patient withdrawals owing to AEs
  - significantly lower in the placebo + MTX group than in all the biologic groups

B. Withdrawals due to adverse events. OR < 1 means that the treatment in the top left cell is better.

Placebo+MTX											
0.98 (0.63 – 1.56)	Sarilumab 150mg+MTX										
0.64 (0.41 – 0.96)	0.65 (0.35 – 1.21)	Tocilizumab 8mg+MTX									
0.59 (0.37 – 0.94)	0.61 (0.31 – 1.12)	0.93 (0.50 – 1.73)	Sirukumab 50mg+MTX								
0.57 (0.37 – 0.95)	0.59 (0.35 – 1.07)	0.90 (0.48 – 1.74)	0.98 (0.48 – 1.94)	Adalimumab							
0.58 (0.36 – 0.90)	0.60 (0.31 – 1.10)	0.90 (0.49 – 1.67)	0.98 (0.64 – 1.48)	1.01 (0.50 – 1.95)	Sirukumab 100mg+MTX						
0.57 (0.31 – 1.02)	0.60 (0.27 – 1.21)	0.90 (0.50 – 1.59)	0.97 (0.46 – 2.03)	0.99 (0.46 – 2.06)	0.98 (0.48 – 2.12)	Tocilizumab 4mg+MTX					
0.51 (0.28 – 1.05)	0.52 (0.25 – 1.28)	0.80 (0.38 – 1.75)	0.88 (0.38 – 2.03)	0.88 (0.44 – 1.95)	0.89 (0.42 – 2.01)	0.90 (0.38 – 2.20)	Sirukumab 100mg				
0.38 (0.24 – 0.61)	0.39 (0.24 – 0.62)	0.60 (0.32 – 1.14)	0.64 (0.34 – 1.25)	0.66 (0.34 – 1.21)	0.65 (0.35 – 1.33)	0.65 (0.32 – 1.42)	0.74 (0.30 – 1.61)	Sarilumab 200mg+MTX			
0.33 (0.18 – 0.60)	0.34 (0.17 – 0.69)	0.52 (0.25 – 1.04)	0.56 (0.26 – 1.18)	0.57 (0.28 – 1.07)	0.57 (0.28 – 1.21)	0.58 (0.25 – 1.27)	0.64 (0.35 – 1.20)	0.88 (0.41 – 1.84)	Sirukumab 50mg		
0.33 (0.21 – 0.53)	0.34 (0.21 – 0.54)	0.52 (0.27 – 0.99)	0.56 (0.29 – 1.09)	0.57 (0.30 – 1.05)	0.56 (0.31 – 1.16)	0.57 (0.28 – 1.23)	0.66 (0.24 – 1.43)	0.87 (0.57 – 1.32)	1.02 (0.47 – 2.20)	Sarilumab 200mg	
0.24 (0.12 – 0.53)	0.25 (0.12 – 0.57)	0.38 (0.17 – 0.90)	0.41 (0.17 – 1.02)	0.42 (0.25 – 0.74)	0.42 (0.18 – 1.02)	0.42 (0.18 – 1.08)	0.47 (0.20 – 1.18)	0.64 (0.28 – 1.53)	0.74 (0.33 – 1.80)	0.73 (0.33 – 1.75)	Tocilizumab

Anmerkung/Fazit der Autoren

Long-term studies are therefore needed to determine the relative efficacy and safety of tocilizumab, sarilumab, and sirukumab in a large number of patients with active RA that inadequately responds to MTX or TNF inhibitors

Kommentare zum Review

No restriction on degree of severity of RA.

ACR response not reported.

Wu ZP et al., 2018 [30].

Efficacy and safety of baricitinib for active rheumatoid arthritis in patients with an inadequate response to conventional synthetic or biological disease-modifying anti-rheumatic drugs: A meta-analysis of randomized controlled trials

Siehe auch Kunwar S et.al, 2018 [18].

Fragestellung

To assess the efficacy and safety of baricitinib for active rheumatoid arthritis (RA) in patients with an inadequate response or intolerance to conventional synthetic or biological disease‐modifying anti‐rheumatic drugs (DMARDs).

Methodik

Population:

- Patients aged >18 years with an inadequate response or intolerance to conventional synthetic or biological DMARDs

Intervention:

- baricitinib

Komparator:

- placebo

Endpunkte:

- The proportion of patients achieving an ACR20;
- the SDAI ≤3.3;
- patient‐reported outcomes (PROs), including the Patient's Global Assessment of Disease Activity (PtGA) and Scores on the Health Assessment Questionnaire‐Disability Index (HAQ‐DI)).
- Adverse events (AEs)
- discontinuation due to AEs,
- infections
- serious infections, including pneumonia and cellulitis.

Recherche/Suchzeitraum:

- Electronic databases, including Medline, Embase Science Direct, Web of Science and the Cochrane library, were searched to retrieve relevant studies published until July 3, 2017.

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

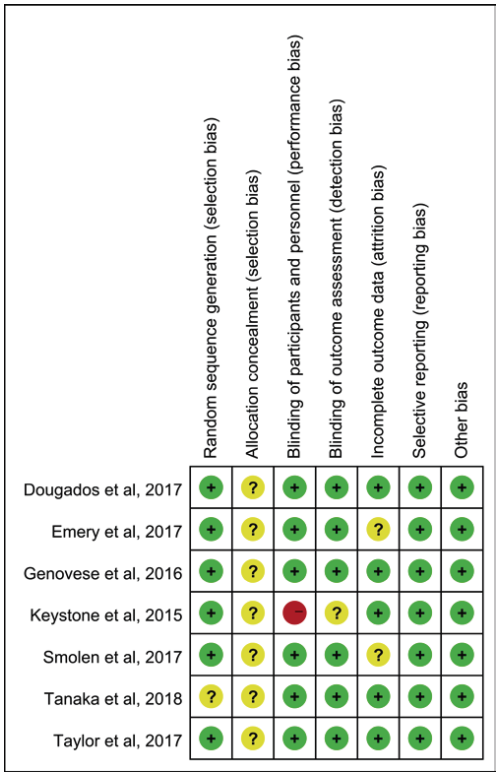
- 7 RCTs were selected, including 2 phase‐II trials and 5 phase‐III trials

Charakteristika der Population:

- dosage of baricitinib ranged from 1 to 8 mg (1, 2, 4 and 8 mg) once daily.
- A total of 4,173 patients were included in this meta‑analysis: 1,371 patients were included in the 4 mg baricitinib group and 1,443 patients were included in placebo group.
- mean age ranged from 51.7 to 57.5 years in the 4 mg group and 49 to 56 years in the placebo group

Qualität der Studien:

Studienergebnisse:



- *implified Disease Activity Index score (SDAI) ≤3.3*: statistically significant improvement in the baricitinib once daily groups compared with that in the placebo group at 12 weeks (4 studies, N(Baricitinib)=943, N(Placebo)=990, RR, 4.57; 95% CI, 2.78‑7.52; P<0.00001, I^2=20%) and at 24 weeks (3 studies, N(Baricitinib)=891, N(Placebo)=892, RR, 4.58; 95% CI, 3.08‑6.82; P<0.00001, I^2=0%)
- *Health Assessment Questionnaire‑Disability Index score (HAQ‑DI):* significant reduction in the HAQ‑DI score with baricitinib compared with placebo group at 12 weeks (2 studies, MD, ‑0.22; 95% CI, ‑(0.30‑0.14); P<0.00001, I^2=0%) and 24 weeks (2 studies, MD, ‑0.26; 95% CI, ‑(0.34‑0.17) (26,29); P<0.00001, I^2=0%)
- *Patient's Global Assessment of Disease Activity (PtGA):* patients receiving baricitinib had lower PtGA scores compared with those in the group receiving placebo at 12 weeks (2 studies, MD, ‑10.99; 95% CI, ‑(14.55‑7.44); P<0.00001, I^2=47%) and 24 weeks (2 studies, MD, ‑12.4; 95% CI, ‑(16.02‑8.77); P<0.00001; I^2=55%)
- *Adverse events:* AEs more frequent in patients receiving baricitinib than in those receiving placebo (12 weeks: 4 studies, RR, 1.08; 95% CI, 0.97‑1.20; P=0.14), 24 weeks observed (3 studies, (RR, 1.13; 95% CI, 1.01‑1.26; P=0.03)

- *discontinuation due to AE:* at 12 weeks (4 studies; RR, 1.15; 95% CI, 0.60‑2.22; P=0.67) (3,24,25,28) and 24 weeks (3 studies; RR, 1.38; 95% CI, 0.90‑2.13; P=0.14
- *infection:* higher risk of infection with baricitinib compared to placebo at 12 weeks (2 studies, n/N(Baricitinib)=114/404, n/N(Placebo)=88/404, RR, 1.30; 95% CI, 1,02-1,65; P=0.04, I^2=0%) and 24 weeks (3 studies, n/N(Baricitinib)=342/891, n/N(Placebo)=268/892, RR, 1.28; 95% CI, 1,12-1,45; P=0.0002, I^2=0%)
- *serious infection:* 12 weeks (3 studies; RR, 0.83; 95% CI, 0.26‑2.71; P=0.76, I^2=0%) and 24 weeks (3 studies; RR, 0.94; 95% CI, 0.47‑1.88; P=0.86, I^2=0%)

Anmerkung/Fazit der Autoren

Baricitinib produced a clinical improvement in the treatment of RA within a short‑term treatment period. Baricitinib (4 mg once daily) was the most effective dosage in patients with an inadequate response to conventional synthetic or biological DMARDs. Nearly all of the laboratory outcomes exhibited significant changes in the baricitinib group compared with the placebo group, but the clinical significance of these changes remains elusive. High‑quality RCTs with long‑term exposure and different populations are required to determine the efficacy and safety of baricitinib.

Bergrath, E et al., 2017 [4].

Tofacitinib versus Biologic Treatments in Moderate-to-Severe Rheumatoid Arthritis Patients Who Have Had an Inadequate Response to Nonbiologic DMARDs: Systematic Literature Review and Network Meta-Analysis

Fragestellung

To compare the efficacy and tolerability of tofacitinib, an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA), as monotherapy and combined with disease-modifying antirheumatic drugs (DMARDs) versus biological DMARDs (bDMARDs) and other novel DMARDs for second-line moderate-to-severe rheumatoid arthritis (RA) patients

Methodik

Population:

- Patients who are intolerant or experience moderate/high disease activity despite traditional, nonbiologic DMARDs (inadequate response [DMARD-IR])
- Trials were excluded if patients were required to fail at least two or more nonbiological DMARDs or if patients had received nonbiological DMARDs with no Indikation of an inadequate response or failure.

Intervention:

- abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, tocilizumab, baricitinib (investigational), and tofacitinib, alone or in combination with MTX, or other nonbiologic DMARDs.

Komparator:

- Placebo or any of the aforementioned interventions

Endpunkte:

- ACR response criteria, HAQ-DI, and rates of discontinuation due to adverse events

Recherche/Suchzeitraum:

- MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) databases were searched simultaneously using Ovid
- Search period: 1990 and March 2015

Qualitätsbewertung der Studien:

- according to the Centre for Reviews and Dissemination of the University of York

Ergebnisse

Anzahl eingeschlossener Studien:

- 45 RCTs

Charakteristika der Population:

- Most studies were double-blind, parallel RCTs.
- The majority of trials were multicentered and multinational: most studies included patient populations predominantly from Europe and North America, although some studies also included patients from South America and Asia.
- In RCTs evaluating efficacy of biologics in combination with a nonbiologic DMARD, MTX was the background treatment of choice.
- Of the 45 trials identified, 11 second-line trials required patients to be DMARD-IR, while 28 trials required patients to be MTX-IR.

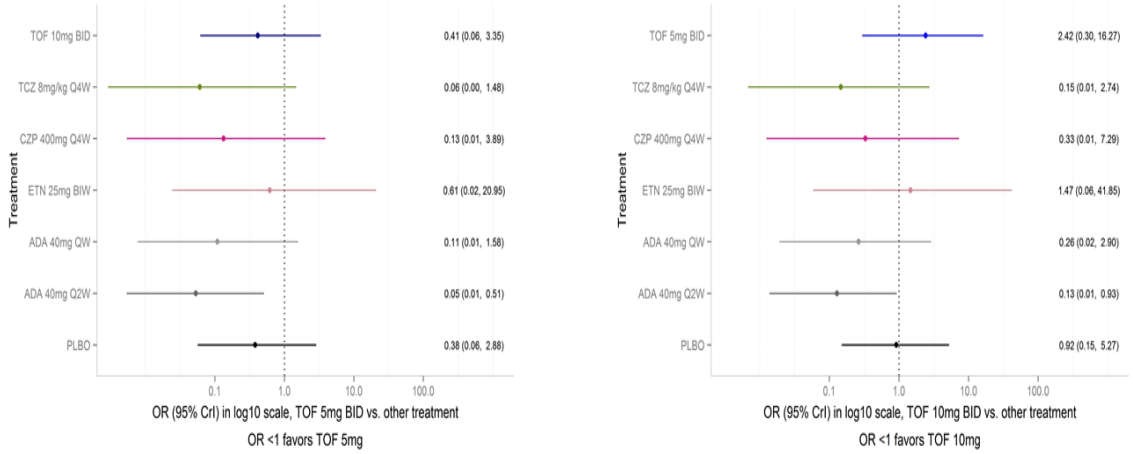
Qualität der Studien:

- Most of the studies demonstrated a low risk of bias

Studienergebnisse:

Monotherapy:

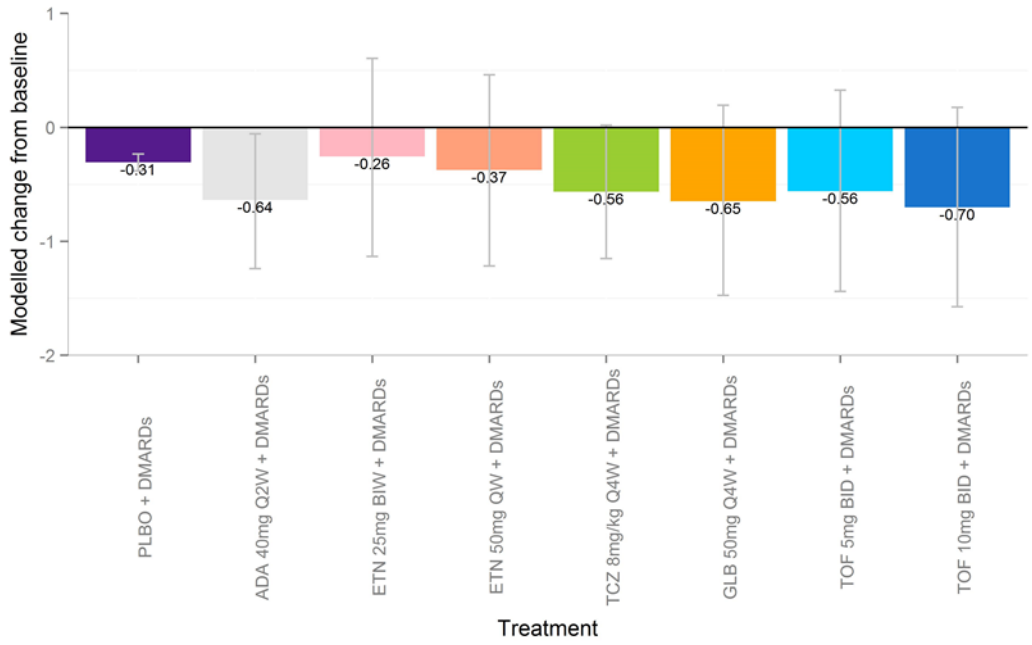
- *Physical Functioning, as Measured by the HAQ-DI*: NMA not feasible due to lack of data
- *Withdrawals due to adverse events*:
  - Tofacitinib 5mg BID / 10 mg BID related withdrawals due to adverse events were favorable to twice weekly adalimumab 40mg (Q2W), comparable to the other monotherapies,



Odds ratios and 95% CIs for TOF 5 mg and TOF 10 mg versus other treatments, as obtained with random effects NMA

Combination Therapy

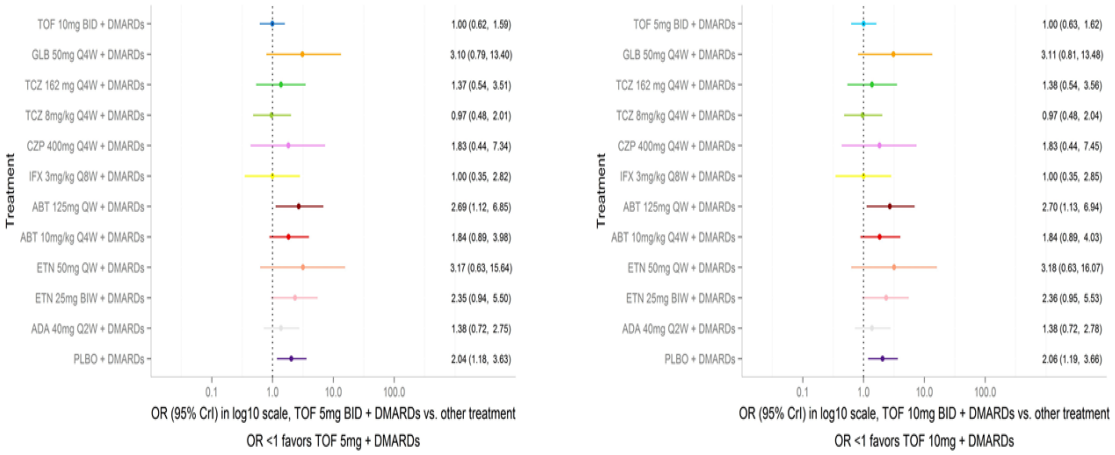
- *Physical Functioning: HAQ-DI*.
  - Statitically significant reduction in HAQ-DI, only observed for adalimumab 40mg (Q2W)+DMARDs
  - The modelled change from baseline in HAQ-DI was greatest for tofacitinib 10mg BID + DMARDs, but not statistically significant



HAQ-DI at 24 weeks (Combination therapies) Modelled change from baseline and 95% CIs for all treatments, as obtained with random effects NMA

- Discontinuation due to Adverse Events
  - Tofacitinib 5mg BID + DMARDs and tofacitinib 10mg + DMARDs were less favorable than placebo + DMARDs and abatacept 125mg QW + DMARDs, but they were

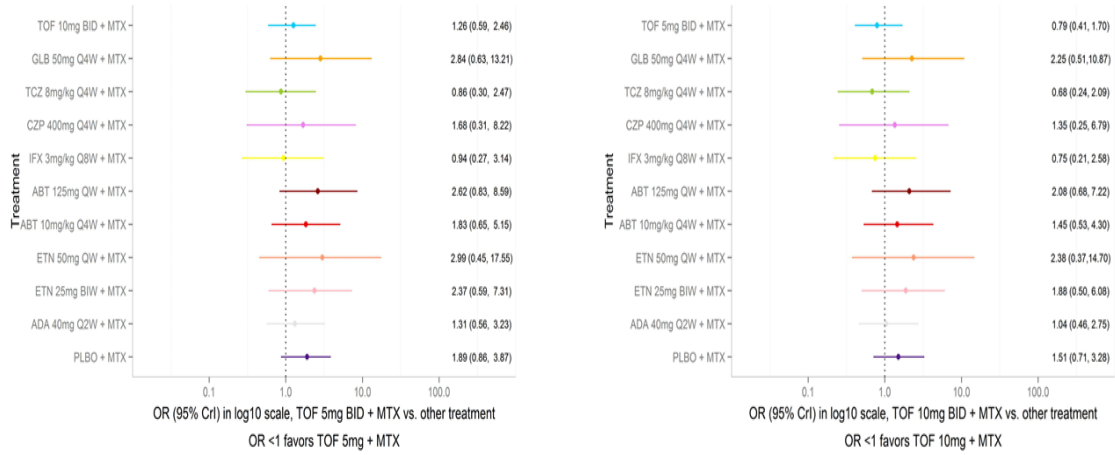
comparable to the other combination therapies with respect to withdrawals due to adverse events



Withdrawals due to adverse events (Combination therapy) - Odds ratios and 95% CIs for TOF 5 mg + DMARDs and TOF 10 mg + DMARDs versus other treatments, as obtained with random effects NMA

MTX Combination Therapy:

- *Physical Functioning: HAQ-DI*:
  - tofacitinib 10mg BID + MTX showed the greatest improvement in HAQ-DI
  - no statitically significant improvement for any MTX combination therapy
- Discontinuation due to adverse events:
  - Both tofacitinib BID dosages in combination withMTX were likely to be less favorable than placebo + MTX, etanercept 25mg BIW + MTX, abatacept 125mg QW+MTX, and golimumab 50mg Q4W + MTX.
  - Tofacitinib 5mg BID + MTX was also likely to be less favorable than etanercept 50mg QW+ MTX and abatacept 10 mg/kg Q4W + MTX



Withdrawals due to adverse events (MTX combination therapy) – Odds ratios and 95% CIs for TOF 5 mg + MTX and TOF 10 mg + MTX versus other treatments, as obtained with random effects NMA

Anmerkung/Fazit der Autoren

Based on currently available RCT evidence, it can be concluded that oral tofacitinib as 5 or 10 mg BID monotherapy has comparable efficacy to currently available biologic agents used for nonbiologic DMARD-IR RA patients in terms of improvements in signs and symptoms and physical function. Based on the synthesis of the evidence available for combination biologic therapies, tofacitinib 5mg BID and tofacitinib 10mg BID in combination with DMARDs or MTX were found to be mostly comparable to other combination therapies in terms of efficacy. Rates of discontinuation from the trials due to adverse events appear comparable for all monotherapies. However, longer-term follow-up data are required to further understand the benefit-risk profile of tofacitinib relative to other combination therapies.

Kommentare zum Review

study and authors were sponsored by Pfizer

ACR response not reported

3.4 Leitlinien

Daien C et al., 2019 [6].

French Society for Rheumatology

Update of French Society for Rheumatology. Recommendations for Managing Rheumatoid Arthritis

Fragestellung:

To update SFR recommendations on managing RA in order to provide patients with optimal management.

Methodik

Grundlage der Leitlinie

- Repräsentatives Leitliniengremium (12 expert rheumatologists, 2 patient self-help group representatives, and an occupational therapist)
- Interessenkonflikte dargelegt, Umgang mit Interessenskonflikten im Konsensusprozess unklar;
- Systematische Suche von Evidenz, Auswahl und Bewertung der Evidenz nicht beschrieben, weiterhin wurden die aktuellen EULAR Empfehlungen bei der Formulierung der Empfehlungen berücksichtigt
- Systematic literature review in MedLine to retrieve data published between completion of the literature review for the earlier recommendations (i.e., between November 2015 and February 2016 depending on the item) and October 2017.
- Formale Konsensusprozesse beschrieben (Each panel member scored each recommendation on a 0-10 scale where 0 indicated complete disagreement and 10 complete agreement.), Anwendung von formalen Konsensusprozess auch im externen Begutachtungsverfahren;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist in Form einer Diskussion dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert

Recherche/Suchzeitraum:

- Systematic literature review in MedLine to retrieve data published between completion of the literature review for the earlier recommendations (i.e., between November 2015 and February 2016 depending on the item) and October 2017.

LoE / GoR

- Oxford Centre for Evidence-based Medicine - Levels of Evidence (March 2009).

Sonstige methodische Hinweise

Process of study selection not described.

Unclear how vote of panel members on 0-10 scale was transformed to % agreement.

Empfehlungen

Table 2. 2018 recommendations of the French Society for Rheumatology (*Société Française de Rhumatologie*, SFR) about the management of rheumatoid arthritis (RA)

General principles and recommendations	Level of evidence	Grade	Agreement, Task force Mean (SD)	Agreement, Review panel Mean (SD)
Second and subsequent treatment lines				
9. In patients with an inadequate response or intolerance to methotrexate, the treatment must be optimized.			9.2 (0.9)	8.4 (2.1)
• In patients with adverse prognostic factors, add-on bDMARD or tsDMARD therapy can be considered, using a TNF□ antagonist, abatacept, an IL-6 pathway antagonist, a JAK inhibitor, or, under specific circumstances, rituximab.[#]	[#]Ib	[#]A		
• In patients without adverse prognostic factors, a switch to another csDMARD (leflunomide, sulfasalazine) or the combination of several csDMARDs can be considered;[§] if this strategy fails or is contraindicated, targeted therapy (with a bDMARD or tsDMARD) should be considered.	[§]V	[§]D		

- Changes to the 2014 version
  - To insist on the need for optimizing the DMARD regimen if the response is inadequate ("must be optimized").
  - tsDMARDs are mentioned in addition to bDMARDs
  - csDMARD combination (previously methotrexate/sulfasalazine/hydroxychloroquine) no longer specified.
- Optimization strategy varies depending on whether the following predictors of a poor prognosis or poor treatment response are present:
  - early erosions
  - RFs and ACPA, notably in high titers (≥3N)
  - persistent moderate-to-high disease activity despite csDMARD therapy, with high ESR and
  - CRP values and/or a high swollen joint count
  - failure of ≥2 csDMARDs
- No studies were specifically designed to compare the efficacy of csDMARDs and targeted therapies depending on the presence or absence of factors of adverse prognostic significance.

- Neither head-to-head comparisons [70–72] nor meta-analyses found any consistent evidence of differences in efficacy across targeted therapies given in combination with methotrexate [6,73,74]
- Among targeted therapies, bDMARDs may deserve preference based on the longer experience with these drugs and availability of long-term registry data on treatment safety [8,75]. Nevertheless, safety data on tsDMARDs are favorable [76,77], and baricitinib may be more effective than adalimumab in combination with methotrexate [72].

[6] Nam JL, Takase-Minegishi K, Ramiro S, Chatzidionysiou K, Smolen JS, van der Heijde D, et al. Efficacy of biological disease-modifying antirheumatic drugs: a systematic literature review informing the 2016 update of the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis 2017;76:1113–36. doi:10.1136/annrheumdis-2016-210713.
[8] Ramiro S, Sepriano A, Chatzidionysiou K, Nam JL, Smolen JS, van der Heijde D, et al. Safety of synthetic and biological DMARDs: a systematic literature review informing the 2016 update of the EULAR recommendations for management of rheumatoid arthritis. Ann Rheum Dis 2017;76:1101–36.
[70] Fleischmann R, Mysler E, Hall S, Kivitz AJ, Moots RJ, Luo Z, et al. Efficacy and safety of tofacitinib monotherapy, tofacitinib with methotrexate, and adalimumab with methotrexate in patients with rheumatoid arthritis (ORAL Strategy): a phase 3b/4, double-blind, head-tohead, randomised controlled trial. Lancet Lond Engl 2017;390:457–68.
[71] Schiff M, Weinblatt ME, Valente R, van der Heijde D, Citera G, Elegbe A, 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.
[72] Taylor PC, Keystone EC, van der Heijde D, Weinblatt ME, Del Carmen Morales L, Reyes Gonzaga J, et al. Baricitinib versus Placebo or Adalimumab in Rheumatoid Arthritis. N Engl J Med 2017;376:652–62.
[73] Nam JL, Takase-Minegishi K, Ramiro S, Chatzidionysiou K, Smolen JS, van der Heijde D, et al. Efficacy of biological disease-modifying antirheumatic drugs: a systematic literature review informing the 2016 update of the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis 2017;76:1113–36.
[74] Singh JA, Hossain A, Tanjong Ghogomu E, 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 metaanalysis (NMA). Cochrane Database Syst Rev 2016;11:CD012437.
[75] de La Forest Divonne M, Gottenberg JE, Salliot C. Safety of biologic DMARDs in RA patients in real life: A systematic literature review and meta-analyses of biologic registers. Jt Bone Spine Rev Rhum 2017;84:133–40.
[76] Cohen SB, Tanaka Y, Mariette X, Curtis JR, Lee EB, Nash P, et al. Long-term safety of tofacitinib for the treatment of rheumatoid arthritis up to 8.5 years: integrated analysis of data from the global clinical trials. Ann Rheum Dis 2017;76:1253–62.
[77] Curtis JR, Xie F, Yun H, Bernatsky S, Winthrop KL. Real-world comparative risks of herpes virus infections in tofacitinib and biologic-treated patients with rheumatoid arthritis. Ann Rheum Dis 2016;75:1843–7.

10. All targeted therapies (bDMARDs* or tsDMARDs#) are best used in combination with methotrexate..	*Ia #Ib	A	9.5 (0.7)	8.9 (2.0)

- Compared to the 2014 version of this recommendation, the term “targeted therapies” is used instead of “biologics”, to include tsDMARDs.
- Added efficacy demonstrated for all bDMARDs [6,83], including tocilizumab, with which the combination produced better numerical results [84–86].
- The same applies to JAK inhibitors [70, 87]

6 & 70: see above.
[83] Buckley F, Finckh A, Huizinga TWJ, Dejonckheere F, Jansen JP. Comparative Efficacy of Novel DMARDs as Monotherapy and in Combination with Methotrexate in Rheumatoid Arthritis Patients with Inadequate Response to Conventional DMARDs: A Network Meta- Analysis. J Manag Care Spec Pharm 2015;21:409–23.
[84] Dougados M, Kissel K, Sheeran T, Tak PP, Conaghan PG, Mola EM, 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.
[85] Burmester GR, Rigby WF, van Vollenhoven RF, Kay J, Rubbert-Roth A, Blanco R, et al. Tocilizumab combination therapy or monotherapy or methotrexate monotherapy in methotrexate-naive patients with early rheumatoid arthritis: 2-year clinical and radiographic results from the randomised, placebo-controlled FUNCTION trial. Ann Rheum Dis 2017;76:1279–84.
[86] Kaneko Y, Atsumi T, Tanaka Y, Inoo M, Kobayashi-Haraoka H, Amano K, et al. Comparison of adding tocilizumab to methotrexate with switching to tocilizumab in patients with rheumatoid arthritis with inadequate response to methotrexate: 52-week results from a prospective, randomised, controlled study (SURPRISE study). Ann Rheum Dis 2016;75:1917–23.
[87] Fleischmann R, Schiff M, van der Heijde D, Ramos-Remus C, Spindler A, Stanislav M, et al. Baricitinib, Methotrexate, or Combination in Patients With Rheumatoid Arthritis and No or Limited Prior Disease-Modifying Antirheumatic Drug Treatment. Arthritis Rheumatol Hoboken NJ 2017;69:506–17.

11. Patients who fail a first targeted therapy (bDMARD or tsDMARD) should be switched to another targeted therapy. In the event of primary failure, a switch to a targeted therapy that has a different mechanism of action may deserve preference.	*Ia §V	A	9.6 (0.6)	9.0 (1.5)

- Compared to the 2014 recommendations:
  - the term “targeted therapy” has been substituted for “biological agent” to include tsDMARDs,
  - a preference for switching to a drug that has a different mechanism of action in the event of primary failure has been added.
- In patients having failed a first TNF antagonist, most studies found that efficacy was similar across targeted therapies, i.e., between switching to another TNF-α antagonist and switching to a drug with a different mechanism of action [6,102,103].
- To date, no published evidence exists about the efficacy of a second JAK inhibitor after failure of a first tsDMARD or about the efficacy of a second IL-6 receptor antagonist after failure of tocilizumab.

6: see above.
[102] Schoels M, Aletaha D, Smolen JS, Wong JB. Comparative effectiveness and safety of biological treatment options after tumour necrosis factor α inhibitor failure in rheumatoid arthritis: systematic review and indirect pairwise meta-analysis. Ann Rheum Dis 2012;71:1303–8.
[103] Manders SHM, Kievit W, Adang E, Brus HL, Moens HJB, Hartkamp A, et al. Costeffectiveness of abatacept, rituximab, and TNFi treatment after previous failure with TNFi treatment in rheumatoid arthritis: a pragmatic multi-centre randomised trial. Arthritis Res Ther 2015;17:134.

Sonstige Hinweise

Treatment flow chart in appendix (Figure 4).

National Institute for Health and Care Excellence (NICE), 2018 [20,21,22].

Rheumatoid arthritis in adults: management

Fragestellung:

This guideline covers diagnosing and managing rheumatoid arthritis. It aims to improve quality of life by ensuring that people with rheumatoid arthritis have the right treatment to slow the progression of their condition and control their symptoms.

Methodik

Grundlage der Leitlinie:

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Entwicklung der Empfehlungen basierend auf klinischer und gesundheitsökonomischer Evidenz
- Informelle Konsensusprozesse und externes Begutachtungsverfahren dargelegt

- Empfehlungen der Leitlinie sind eindeutig, Verbindung zu der zugrundeliegenden Evidenz ist nicht immer eindeutig dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- Evidence report F DMARDs describes relevant systematic evidence review (searches in Medline & Embase until Oct 2017)

LoE / GoR

- Own checklists for quality assessment and application of GRADE
- GoR reflected in wording:
  - The strength of the recommendation (for example the word ‘offer’ was used for strong recommendations and ‘consider’ for weaker recommendations).
  - "To avoid giving the impression that higher grade recommendations are of higher priority for implementation, NICE no longer assigns grades to recommendations".

Sonstige methodische Hinweise

Although the guideline is dated July 2018, most recommendations for drug therapy have not been changed since 2009.

Cited evidence of recommendations often NICE technology appraisal guidance. No further link between evidence and recommendation.

Empfehlungen

1.5 Further pharmacological management

Biological and targeted synthetic DMARDs

The recommendations below are from NICE technology appraisal guidance 72. The 2009 guideline committee reviewed the evidence on anakinra and incorporated the recommendations into the guideline. The technology appraisal was then withdrawn.

- 1.5.1 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. [2009]
- 1.5.2 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. [2009]
- 1.5.3 Do not offer the combination of tumour necrosis factor-α (TNF-α) inhibitor therapy and anakinra for RA. [2009]

Glucocorticoids

- 1.5.4 Offer short-term treatment with glucocorticoids for managing flares in adults with recent-onset or established disease to rapidly decrease inflammation. [2009]
- 1.5.5 In adults 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 and targeted synthetic DMARDs) have been offered. [2009, amended 2018]

Inadequate response to conventional DMARDs

Biologicals: Sarilumab

- The following recommendations are an extract from NICE technology appraisal guidance on sarilumab for moderate to severe rheumatoid arthritis.
- Sarilumab, with methotrexate, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to intensive therapy with a combination of conventional DMARDs, only if:
  - disease is severe (a DAS28 of more than 5.1) […].
- Sarilumab can be used as monotherapy for people who cannot take methotrexate because it is contraindicated or because of intolerance, when the criteria above are met.

Why we made the recommendations on sarilumab:

- Clinical trials showed sarilumab plus methotrexate or conventional DMARDs to be more effective than methotrexate or conventional DMARDs for treating moderate to severe active rheumatoid arthritis that has not responded adequately to conventional DMARDs. The trials also showed that for treating severe active rheumatoid arthritis that has not responded adequately to conventional DMARDs, sarilumab alone is more effective than adalimumab alone.

Biologicals: Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept

- The following recommendations are from NICE technology appraisal guidance on adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed.
- Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept, all in combination with methotrexate, are recommended as options for treating rheumatoid arthritis, only if:
  - disease is severe, that is, a DAS28 greater than 5.1 and
  - disease has not responded to intensive therapy with a combination of conventional DMARDs […].
- Adalimumab, etanercept, certolizumab pegol or tocilizumab can be used as monotherapy for people who cannot take methotrexate because it is contraindicated or because of intolerance, when the criteria above are met.

Biologicals: Anakinra

- On the balance of its clinical benefits and cost effectiveness, anakinra is not recommended for the treatment of rheumatoid arthritis […].
- Patients currently receiving anakinra for rheumatoid arthritis 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.

- Do not offer the combination of TNF-α inhibitor therapy and anakinra for RA.

Other immunomodulatory therapies: Tofacitinib

- The following recommendations are an extract from NICE technology appraisal guidance on tofacitinib for moderate to severe rheumatoid arthritis.
- Tofacitinib, with methotrexate, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to intensive therapy with a combination of conventional DMARDs, only if:
  - disease is severe (a DAS28 of more than 5.1) […].
- Tofacitinib can be used as monotherapy for adults who cannot take methotrexate because it is contraindicated or because of intolerance, when the criteria above are met.

Why we made the recommendations on tofacitinib:

- Clinical trial evidence shows tofacitinib plus conventional DMARDs is more effective than conventional DMARDs alone for treating moderate and severe active rheumatoid arthritis that has not responded adequately to conventional or biological DMARDs.
- Clinical trial evidence also shows that tofacitinib plus methotrexate is not worse in effectiveness than the biological DMARD adalimumab plus conventional DMARDs in people whose disease has responded inadequately to conventional DMARDs.

Other immunomodulatory therapies: Baricitinib

- The following recommendations are an extract from NICE's technology appraisal guidance on baricitinib for moderate to severe rheumatoid arthritis.
- Baricitinib, with methotrexate, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to intensive therapy with conventional DMARDs, only if:
  - disease is severe (a DAS28 of more than 5.1) […].
- Baricitinib can be used as monotherapy for people who cannot take methotrexate because it is contraindicated or because of intolerance, when the above criteria are met.

Why we made the recommendations on baricitinib

- Clinical trials showed baricitinib plus conventional DMARDs to be more effective than conventional DMARDs alone for treating severe active rheumatoid arthritis that has not responded adequately to conventional or biological DMARDs
- Baricitinib plus conventional DMARDs was also shown to have similar effectiveness to the biological DMARD adalimumab in people whose disease has responded inadequately to conventional DMARDs.

Inadequate response or intolerance to biological DMARDs, and rituximab is suitable

Rituximab

- The following recommendations are an extract from NICE technology appraisal guidance on adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor.
- Rituximab in combination with methotrexate is recommended as an option for the treatment of adults with severe active rheumatoid arthritis who have had an inadequate response to, or are intolerant of, other DMARDs, including at least one TNF inhibitor.

Inadequate response or intolerance to biological DMARDs, and rituximab is not suitable

Biologicals: Sarilumab

- The following recommendations are an extract from NICE technology appraisal guidance on sarilumab for moderate to severe rheumatoid arthritis.
- Sarilumab, with methotrexate, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to or who cannot have other DMARDs, including at least 1 biological DMARD, only if:
  - disease is severe (a DAS28 of more than 5.1) and
  - they cannot have rituximab […].
- Sarilumab can be used as monotherapy for people who cannot take methotrexate because it is contraindicated or because of intolerance, when the criteria above are met.

Biologicals: Adalimumab, etanercept, infliximab and abatacept

- The following recommendations are an extract from NICE technology appraisal guidance on adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor.
- Adalimumab, etanercept, infliximab and abatacept, each in combination with methotrexate, are recommended as treatment options only for adults with severe active rheumatoid arthritis who have had an inadequate response to, or have an intolerance of, other DMARDs, including at least one TNF inhibitor, and who cannot receive rituximab therapy because they have a contraindication to rituximab, or when rituximab is withdrawn because of an adverse event.
- Adalimumab monotherapy and etanercept monotherapy are recommended as treatment options for adults with severe active rheumatoid arthritis who have had an inadequate response to, or have an intolerance of, other DMARDs, including at least one TNF inhibitor, and who cannot receive rituximab therapy because they have a contraindication to methotrexate, or when methotrexate is withdrawn because of an adverse event.

Biologicals: Golimumab

- The following recommendations are from NICE technology appraisal guidance on golimumab for the treatment of rheumatoid arthritis after the failure of previous disease-modifying anti-rheumatic drugs.
- Golimumab in combination with methotrexate is recommended as an option for the treatment of rheumatoid arthritis in adults whose rheumatoid arthritis has responded inadequately to other DMARDs, including a TNF inhibitor, if:
  - it is used as described for adalimumab, etanercept, infliximab, rituximab and abatacept (NICE technology appraisal guidance 195) […].

Biologicals: Certolizumab pegol

- The following recommendations are from NICE technology appraisal guidance on certolizumab pegol for treating rheumatoid arthritis after inadequate response to a TNF-alpha inhibitor.
- Certolizumab pegol, in combination with methotrexate, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to, or who cannot tolerate, other DMARDs including at least 1 TNF-alpha inhibitor, only if:

  - disease activity is severe and
  - rituximab is contraindicated or not tolerated […].
- Certolizumab pegol, as monotherapy, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to, or who cannot tolerate, other DMARDs including at least 1 TNF-alpha inhibitor, only if:
  - disease is severe and
  - rituximab therapy cannot be given because methotrexate is contraindicated or not tolerated […].

Biologicals: Tocilizumab

- The following recommendations are from NICE technology appraisal guidance on tocilizumab for the treatment of rheumatoid arthritis.
- Tocilizumab in combination with methotrexate is recommended as an option for the treatment of rheumatoid arthritis in adults if:
  - the disease has responded inadequately to DMARDs and a TNF inhibitor and the person cannot receive rituximab because of a contraindication to rituximab, or because rituximab is withdrawn because of an adverse event, and tocilizumab is used as described for adalimumab, etanercept, infliximab and abatacept (NICE technology appraisal guidance 195) […].

Other immunomodulatory therapies: Tofacitinib

- The following recommendations are an extract from NICE's technology appraisal guidance on tofacitinib for moderate to severe rheumatoid arthritis.
- Tofacitinib, with methotrexate, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to, or who cannot have, other DMARDs, including at least 1 biological DMARD, only if:
  - disease is severe (a DAS28 of more than 5.1) and
  - they cannot have rituximab […].
- Tofacitinib can be used as monotherapy for adults who cannot take methotrexate because it is contraindicated or because of intolerance, when the criteria above are met.

Other immunomodulatory therapies: Baricitinib

- The following recommendations are an extract from NICE's technology appraisal guidance on baricitinib for moderate to severe rheumatoid arthritis.
- Baricitinib, with methotrexate, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to or who cannot have other DMARDs, including at least 1 biological DMARD, only if:
  - disease is severe (a DAS28 of more than 5.1) and
  - they cannot have rituximab […].
- Baricitinib can be used as monotherapy for people who cannot take methotrexate because it is contraindicated or because of intolerance, when the above criteria are met.

Inadequate response to rituximab and other biological DMARDs

Biologicals: Sarilumab

- The following recommendations are an extract from NICE technology appraisal guidance on sarilumab for moderate to severe rheumatoid arthritis.
- Sarilumab, with methotrexate, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to rituximab and at least 1 biological DMARD, only if:
  - disease is severe (a DAS28 of more than 5.1) […].

Biologicals: Tocilizumab

- The following recommendations are from NICE technology appraisal guidance on tocilizumab for the treatment of rheumatoid arthritis.
- Tocilizumab in combination with methotrexate is recommended as an option for the treatment of rheumatoid arthritis in adults if:
  - the disease has responded inadequately to one or more TNF inhibitor treatments and to rituximab.

Referenzen aus Leitlinien

Sarilumab for moderate to severe rheumatoid arthritis (2017) NICE technology appraisal guidance 485
Tofacitinib for moderate to severe rheumatoid arthritis (2017) NICE technology appraisal guidance 480
Baricitinib for moderate to severe rheumatoid arthritis (2017) NICE technology appraisal guidance 466
Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed (2016) NICE technology appraisal guidance 375
Certolizumab pegol for treating rheumatoid arthritis after inadequate response to a TNF-alpha inhibitor (2016) NICE technology appraisal guidance 415
Tocilizumab for the treatment of rheumatoid arthritis (2012) NICE technology appraisal guidance 247
Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease-modifying anti-rheumatic drugs (2011) NICE technology appraisal guidance 225
Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (2010) NICE technology appraisal guidance 195

Fiehn C et al., 2018 [7,8].

Deutsche Gesellschaft für Rheumatologie e.V. (DGRh)

S2e-Leitline: Therapie der rheumatoiden Arthritis mit krankheitsmodifizierenden Medikamenten

Fragestellung:

- Hintergrund: Medikamentöse Therapiestrategien zur Behandlung der rheumatoiden Arthritis sind entscheidend für den Langzeitverlauf. Sie dienen dem Ziel, durch frühe und konsequente Unterdrückung der Entzündung Gelenkzerstörung zu verhindern und damit die Funktion zu erhalten.
- Ziel der Arbeit: Erarbeitung eines Konsenses für evidenzbasierte Empfehlungen zur Behandlung der rheumatoiden Arthritis mit krankheitsmodifizierenden Medikamenten in Deutschland.

Methodik

Grundlage der Leitlinie:

- Leitliniengremium aus Fachärzten für internistische Rheumatologie und Orthopädie, sowie einem Patientenvertreter
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- strukturierten Konsensprozess mit Unterstützung von externen, speziell geschulten Moderatoren der AWMF, externe Begutachtung durch den Vorstand der Deutschen Gesellschaft für Rheumatologie
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert

Recherche/Suchzeitraum:

- Durchführung einer systematischen Literaturrecherche: Medline (PubMed), Cochrane Library sowie Embase für den Zeitraum 01.01.2013 bis 21.03.2016 + diverse nachträgliche Recherchen

LoE / GoR

- Empfehlungsgrade nach der Systematik des Oxford Centre for Evidence-Based Medicine von 2009

Sonstige methodische Hinweise

Prozess der Literaturauswahl nicht nachvollziehbar. Nach Ti/Ab-Screening 9884 Abstracts „offen“. Diverse nachträgliche Recherchen und Hinzufügen von Literatur. Auswahl von finalen 30 Volltexten nicht transparent dargestellt.

Empfehlungen sind mit einem Empfehlungsgrad, keinem Evidenzgrad versehen.

Empfehlungen

Empfehlung 5

Falls MTX nicht einsetzbar ist (z.B. wegen Kontraindikationen), soll eine Therapie mit Leflunomid oder mit Sulfasalazin begonnen werden. (Empfehlungsgrad A)

Hintergrund

- Für den Vergleich MTX vs. Leflunomid existiert eine Metaanalyse auf der Basis von 4 RCTs, welche die Gleichwertigkeit beider Substanzen belegt [42] (LoE 1a).
- In einem Placebo-kontrollierten RCT wurden Leflunomid und Sulfasalazin miteinander verglichen und boten ebenfalls gleiche Wirksamkeit [95] (LoE 1b).

42. Golicki D, Newada M, Lis J et al. (2012) Leflunomide in monotherapy of rheumatoid arthritis: meta-analysis of randomized trials. Pol Arch Med Wewn 122:22-32
95. Smolen JS, Kalden JR, Scott DL et al. (1999) Efficacy and safety of leflunomide compared with placebo and sulphasalazine in active rheumatoid arthritis: a double-blind, randomised, multicentre trial. European Leflunomide Study Group. Lancet 353:259-266

Empfehlung 7

Bei Verfehlen des Therapieziels mit der optimierten Starttherapie soll die Therapie eskaliert werden. Bei Fehlen von ungünstigen Prognosefaktoren und moderater Krankheitsaktivität kann eine Kombination mehrerer csDMARDs eingesetzt werden. Bei hoher Krankheitsaktivität und/oder Vorliegen ungünstiger Prognosefaktoren soll die Kombination eines csDMARD (in der Regel MTX) mit einem bDMARD oder tsDMARD zum Einsatz kommen. (Empfehlungsgrad A)

Hintergrund

- Fehlen negative Prognosefaktoren, kann zu Woche 12 bzw. 24 eine Änderung der csDMARD-Strategie erwogen werden.
  - Eine Kombinationstherapie verschiedener csDMARD-Therapien, die MTX beinhaltet, ist in dieser Situation einem Wechsel auf eine MTX-freie csDMARD-Therapie vorzuziehen [63].
  - Die robusteste Datenlage besteht für eine Kombinationstherapie verschiedener csDMARDs nach dem s.g. O´Dell-Schema, bestehend aus MTX/SSZ/HCQ [50], wobei es keinen direkten Vergleich gegen die auch häufig angewandte Kombination aus MTX/ LEF gibt.
  - Im Falle einer frühen MTX-Intoleranz sollte eine alternative csDMARD-Therapie gewählt werden.
- Beim Vorliegen ungünstiger Prognosefaktoren sollte bei Verfehlen des Therapiezieles unter optimierter bereits früher eine Therapie mit einem bDMARD oder einem tsDMARD erwogen werden
  - Eine Präferenz für die eine oder andere Substanzgruppe kann an dieser Stelle nicht ausgesprochen werden (siehe Empfehlung 8).
  - Auf Grund der längeren Erfahrung kommen bisher nach dem ersten csDMARD-Versagen bevorzugt bDMARDs zur Anwendung.
  - Alle bDMARDs oder tsDMARDs sollten, sofern möglich mit MTX kombiniert werden (siehe auch Empfehlung 9).

Tab. 2. Mögliche Prädiktoren für eine schlechtere Prognose

Prädiktor	Referenz	Evidenzgrad
Nach einer csDMARD-Therapie weiterbestehende, moderate oder hohe Krankheitsaktivität gemäß akzeptierter Indizes	[94]	1b
Hohe Akute-Phase-Reaktion (z.B. C-reaktives Protein oder BSG)	[99, 119]	1b, 2
Hohe Anzahl geschwollener Gelenke	[99, 119]	1b, 2
Nachweis von RF und/oder CCP Antikörper	[99, 114, 119]	1b, 2, 2
Initial hoher DAS28-Score	[79]	2
Nachweis von frühen Erosionen	[99]	1b,
Versagen von 2 oder mehreren csDMARDs	[62]	2

50. Hazlewood GS, Barnabe C, Tomlinson G et al. (2016) 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 353:i1777
62. Kiely P, Walsh D, Williams R et al. (2011) Outcome in rheumatoid arthritis patients with continued conventional therapy for moderate disease activity--the early RA network (ERAN). Rheumatology (Oxford) 50:926-931
63. Klarenbeek NB, Guler-Yuksel M, Van Der Kooij SM et al. (2011) 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 70:1039-1046
79. Naredo E, Valor L, De La Torre I et al. (2015) Predictive value of Doppler ultrasound-detected synovitis in relation to failed tapering of biologic therapy in patients with rheumatoid arthritis. Rheumatology (Oxford) 54:1408-1414
94. Smolen JS, Han C, Van Der Heijde DM et al. (2009) Radiographic changes in rheumatoid arthritis patients attaining different disease activity states with methotrexate monotherapy and infliximab plus methotrexate: the impacts of remission and tumour necrosis factor blockade. Ann Rheum Dis 68:823-827
99. Smolen JS, Van Der Heijde DM, St Clair EW et al. (2006) Predictors of joint damage in patients with early rheumatoid arthritis treated with high-dose methotrexate with or without concomitant infliximab: results from the ASPIRE trial. Arthritis Rheum 54:702-710
114. Van Der Heijde DM, Van Riel PL, Van Leeuwen MA et al. (1992) Prognostic factors for radiographic damage and physical disability in early rheumatoid arthritis. A prospective follow-up study of 147 patients. Br J Rheumatol 31:519-525
119. Van Leeuwen MA, Van Rijswijk MH, Sluiter WJ et al. (1997) Individual relationship between progression of radiological damage and the acute phase response in early rheumatoid arthritis. Towards development of a decision support system. J Rheumatol 24:20-27

Empfehlung 8

Nach unzureichendem Ansprechen zweier csDMARD-Therapien soll eine bDMARD- oder tsDMARD-Therapie zum Einsatz kommen. (Empfehlungsgrad A)

Hintergrund

- Der sequentielle Einsatz mehrerer csDMARDs bzw. csDMARD-Kombinationen führt nach den Ergebnissen der BeST-Studie und aus der britischen ERAN-Kohorte spätestens ab dem 2. Wechsel nur noch zu einem sehr geringen Zuwachs an Respondern.
- Bei Verzicht auf eine Eskalation in Form von zielgerichteten Therapien mit bDMARD oder tsDMARD kommt es in einem großen Anteil zum Nichterreichen der Therapieziele [41, 62] (LoE 2).

- Darüber hinaus ergibt sich mit der Anzahl der erfolglosen Wechsel ein beträchtlicher Zeitverlust, der eine vermehrte radiologische Destruktion [41] und dauerhaft einen eingeschränkten Funktionsstatus [62] mit sich bringt.
- Welches bDMARD oder tsDMARD verwendet wird, kann in Anbetracht der Gleichwertigkeit der zur Verfügung stehenden Substanzen individuell (z.B. anhand patientenindividueller Kriterien) entschieden werden.
- tsDMARDs, derzeit namentlich die JAK-Inhibitoren (JAKi) Tofacitinib und Baricitinib, sind eine gleichwertige alternative Therapieoption zu bDMARDs nach Versagen einer csDMARD-Therapie (LoE 1b) [23, 34, 64, 108, 113, 120)

23. Dougados M, Van Der Heijde D, Chen YC et al. (2017) Baricitinib in patients with inadequate response or intolerance to conventional synthetic DMARDs: results from the RA-BUILD study. Ann Rheum Dis 76:88-95
34. Fleischmann R, Kremer J, Cush J et al. (2012) Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. N Engl J Med 367:495-507
41. Goekoop-Ruiterman YP, De Vries-Bouwstra JK, Allaart CF et al. (2007) Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial. Ann Intern Med 146:406-415
62. Kiely P, Walsh D, Williams R et al. (2011) Outcome in rheumatoid arthritis patients with continued conventional therapy for moderate disease activity--the early RA network (ERAN). Rheumatology (Oxford) 50:926-931
64. Kremer J, Li ZG, Hall S et al. (2013) Tofacitinib in combination with nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis: a randomized trial. Ann Intern Med 159:253-261
108. Taylor PC, Keystone EC, Van Der Heijde D et al. (2017) Baricitinib versus Placebo or Adalimumab in Rheumatoid Arthritis. N Engl J Med 376:652-662
113. Van Der Heijde D, Tanaka Y, Fleischmann R et al. (2013) Tofacitinib (CP-690,550) in patients with rheumatoid arthritis receiving methotrexate: twelve-month data from a twenty-four-month phase III randomized radiographic study. Arthritis Rheum 65:559-570
120. Van Vollenhoven RF, Fleischmann R, Cohen S et al. (2012) Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. N Engl J Med 367:508-519

Empfehlung 9

Jede bDMARD- und tsDMARD-Therapie soll wenn möglich mit MTX kombiniert werden. (Empfehlungsgrad A)

Hintergrund

- Für alle bDMARDs und tsDMARDs liegen Studienergebnisse vor, die Vorteile für die Kombination mit MTX im Vergleich zu monotherapeutischem Einsatz zeigen (Übersicht unter [15, 77], LoE 1a).
- MTX sollte daher bei fehlenden Kontraindikationen zumindest so lange kombiniert werden, bis eine anhaltende Remission vorliegt.
- Steht MTX als Kombinationspartner nicht zur Verfügung, so liegen für die IL-6-Rezeptor-Inhibitoren Tocilizumab und Sarilumab als auch für das tsDMARD Baricitinib die besten Monotherapie-Ergebnisse vor:
  - Tocilizumab hat in zahlreichen Studien eine gute monotherapeutische Wirkung bewiesen (Übersicht unter [16, 77]) und sich ebenso wie Sarilumab im Head-to-Head-Vergleich mit Adalimumab als monotherapeutisch überlegen erwiesen [12, 37] (LoE 1b).
  - Baricitinib zeigt klinisch in der Monotherapie die gleiche Wirksamkeit wie in Kombination mit MTX, die Kombination bietet jedoch im radiologischen Outcome noch Vorteile [36] (Evidenzgrad 1).
  - Im Fall von Tofacitinib zeigt eine neue, erst nach der systematischen Literaturrecherche publizierte Vergleichsstudie mit Adalimumab, dass Tofacitinib nur in Kombination mit MTX, nicht aber als Monotherapie, gleichwertig zu Adalimumab ebenfalls in Kombination mit MTX ist. [35]
  - JAKi sollten deswegen mit csDMARDs kombiniert werden (Evidenzgrad 5).

- Für die Anwendung anderer csDMARDs als Kombinationspartner für bDMARDs oder tsDMARDs ist die Evidenz bisher sehr begrenzt

12. Burmester GR, Lin Y, Patel R et al. (2017) Efficacy and safety of sarilumab monotherapy versus adalimumab monotherapy for the treatment of patients with active rheumatoid arthritis (MONARCH): a randomised, double-blind, parallel-group phase III trial. Ann Rheum Dis 76:840-847
15. Chatzidionysiou K, Emamikia S, Nam J et al. (2017) Efficacy of glucocorticoids, conventional and targeted synthetic disease-modifying antirheumatic drugs: a systematic literature review informing the 2016 update of the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis 76:1102-1107
16. Combe B, Landewe R, Daien CI et al. (2017) 2016 update of the EULAR recommendations for the management of early arthritis. Ann Rheum Dis 76:948-959
37. Gabay C, Emery P, Van Vollenhoven R et al. (2013) Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. Lancet 381:1541-1550
77. Nam JL, Takase-Minegishi K, Ramiro S et al. (2017) Efficacy of biological disease-modifying antirheumatic drugs: a systematic literature review informing the 2016 update of the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis 76:1113-1136

Empfehlung 10

Bei nicht ausreichendem Ansprechen (Verfehlen des Therapieziels) oder Unverträglichkeit der ersten bDMARD-Therapie soll der Wechsel auf ein alternatives bDMARD mit gleichem oder anderem Wirkprinzip oder auf ein tsDMARD erfolgen. Ein nochmaliger Wechsel ohne Änderung des Wirkprinzips ist nicht sinnvoll. (Empfehlungsgrad A) Wird die Therapie nach csDMARDs mit einem tsDMARD anstatt einem bDMARD begonnen, so sollte bei Nichtansprechen auf ein bDMARD gewechselt werden. (Empfehlungsgrad D)

Hintergrund

- Gute Ergebnisse sind in kontrollierten Studien für alle 3 Möglichkeiten in RCTs, Register-Auswertungen und Metaanalysen gezeigt worden, formell allerdings nur nach Versagen einer TNF-Inhibitor-Therapie [10, 38, 47, 48, 93, 96] (LoE 1b).
- Eine bessere Wirkung bei Wechsel des Wirkmechanismus nach vorheriger erfolgloser anti-TNF-Therapie wird durch eine randomisierte Studie mit offenem Design nahegelegt [43] (LoE 2).
- Für den Einsatz von JAKi nach Versagen von nicht-TNF-Biologika liegen keine ausreichenden Studiendaten vor.
- Eine evidenzbasierte Empfehlung für das weitere Vorgehen, nachdem ein tsDMARD kein ausreichendes Ansprechen gezeigt hat, kann bisher nicht gegeben werden.

10. Burmester GR, Blanco R, Charles-Schoeman C et al. (2013) 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 381:451-460
38. Genovese MC, Kremer J, Zamani O et al. (2016) Baricitinib in Patients with Refractory Rheumatoid Arthritis. N Engl J Med 374:1243-1252
43. Gottenberg JE, Brocq O, Perdriger A et al. (2016) Non-TNF-Targeted Biologic vs a Second Anti-TNF Drug to Treat Rheumatoid Arthritis in Patients With Insufficient Response to a First Anti-TNF Drug: A Randomized Clinical Trial. JAMA 316:1172-1180
47. Harrold LR, Reed GW, Kremer JM et al. (2015) 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 74:430-436
48. Harrold LR, Reed GW, Solomon DH et al. (2016) Comparative effectiveness of abatacept versus tocilizumab in rheumatoid arthritis patients with prior TNFi exposure in the US Corrona registry. Arthritis Res Ther 18:280
93. Smolen JS, Burmester GR, Combe B et al. (2016) Head-to-head comparison of certolizumab pegol versus adalimumab in rheumatoid arthritis: 2-year efficacy and safety results from the randomised EXXELERATE study. Lancet 388:2763-2774
96. Smolen JS, Kay J, Doyle MK et al. (2009) 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 374:210-221

Sonstige Hinweise

Therapiealgorithmus im Anhang dargestellt (Figure 1).

Smolen JS et al., 2017 [5,19,23,29].

European League Against Rheumatism (EULAR)

EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update

Fragestellung

Updating the 2010 EULAR recommendations for the management of RA.

Methodik

Grundlage der Leitlinie:

- Interdisziplinäres Leitliniengremium (50 individuals, including rheumatologists, health professionals, patient representative)
- Interessenkonflikte dargelegt, Umgang mit Interessenskonflikten im Konsensusprozess unklar;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist in Form einer Diskussion dargestellt;
- Überprüfung der Aktualität nicht beschrieben.

Recherche/Suchzeitraum:

- 3 systematic reviews to different pharmaceutical research questions:
  - Searches for efficacy of glucocorticoids, conventional and targeted synthetic disease-modifying antirheumatic drugs in MEDLINE, EMBASE and CENTRAL from Jan 2013 - Feb 2016
  - Searches for efficacy of biological disease-modifying antirheumatic drugs in MEDLINE, EMBASE and CENTRAL from Jan 2013 - Feb 2016
  - Searches for safety of synthetic and biological DMARDs in MEDLINE, EMBASE and CENTRAL until 9 March 2016

LoE / GoR

- Based on the recommendations of the Oxford Centre for Evidence-Based Medicine
- GoR = 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

Empfehlungen

5.	In patients with a contraindication to MTX (or early intolerance), leflunomide or sulfasalazine should be considered as part of the (first) treatment strategy
6.	Short-term glucocorticoids should be considered when initiating or changing csDMARDs, in different dose regimens and routes of administration, but should be tapered as rapidly as clinically feasible
7.	If the treatment target is not achieved with the first csDMARD strategy, in the absence of poor prognostic factors, other csDMARDs should be considered
8.	If the treatment target is not achieved with the first csDMARD strategy, when poor prognostic factors are present, addition of a bDMARD*[1,2] or a tsDMARD*[3] should be considered; current practice would be to start a bDMARD[§]
9.	bDMARDs*[1,2] and tsDMARDs[#3] should be combined with a csDMARD; in patients who cannot use csDMARDs as comedication, IL-6 pathway inhibitors and tsDMARDs may have some advantages compared with other bDMARDs
10.	If a bDMARD* or tsDMARD[§] has failed, treatment with another bDMARD or a tsDMARD should be considered; if one TNF-inhibitor therapy has failed, patients may receive another TNF-inhibitor or an agent with another mode of action

	LoE	SoR	Final vote (%)	Level of agreement (0–10)
5.	1a	A	85	9.0
6.	1a	A	98	8.7
7.	5	D	94	8.5
8.	*1b §5	*A §D	96	9.0
9.	*1a #1b	*A #A	96	9.2
10.	*1a §5	A* §D	71	9.1
11.	2b	B	86	9.0
12.	4	C	86	8.5

Recommendation 5: […] no new trials have been performed to disprove the previous conclusions.

Recommendation 6:

- The added efficacy of GC when combined with csDMARDs is well established. Indeed, hitherto all trials comparing GC plus csDMARD with bDMARDs plus csDMARD revealed similar efficacy.[146 147]
- The fact that csDMARDs are mentioned specifically implies that GC are typically not needed as a bridging therapy when bDMARDs or tsDMARDs are used, as these usually have a rapid onset of action and the infection risks may be potentiated. [149 150]

146 Goekoop-Ruiterman YP, De Vries-Bouwstra JK, Allaart CF, 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.
147 Nam JL, Villeneuve E, Hensor EM, et al. Remission induction comparing infliximab and high-dose intravenous steroid, followed by treat-to-target: a double-blind, randomised, controlled trial in new-onset, treatment-naive, rheumatoid arthritis (the IDEA study). Ann Rheum Dis 2014;73:75–85.

149 Listing J, Kekow J, Manger B, et al. Mortality in rheumatoid arthritis: the impact of disease activity, treatment with glucocorticoids, TNFα inhibitors and rituximab. Ann Rheum Dis 2015;74:415–21.
150 Lahiri M, Dixon WG. Risk of infection with biologic antirheumatic therapies in patients with rheumatoid arthritis. Best Pract Res Clin Rheumatol 2015;29:290–305.

Recommendation 7:

- It is essentially worded as former recommendation 8,
- 'change to another csDMARD strategy should be considered' reworded, in light of the fact that combination with GC has now been recommended clearly also for this step of the treatment algorithm (item 6) and combinations of csDMARDs are not specifically recommended as initial treatment strategy anymore.

Table 1 Glossary and definitions

Term	Definition
Poor prognostic factors	▶ Moderate (after csDMARD therapy) to high disease activity according to composite measures[71] ▶ High acute phase reactant levels[72 73] ▶ High swollen joint counts[72–74] ▶ Presence of RF and/or ACPA, especially at high levels[72 75] ▶ Combinations of the above[69 76] ▶ Presence of early erosions[72] ▶ Failure of two or more csDMARDs[77]

69 Vastesaeger N, Xu S, Aletaha D, et al. A pilot risk model for the prediction of rapid radiographic progression in rheumatoid arthritis. Rheumatology (Oxford) 2009;48:1114–21.
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77 Kiely P, Walsh D, Williams R, et al. Outcome in rheumatoid arthritis patients with continued conventional therapy for moderate disease activity—the early RA network (ERAN). Rheumatology (Oxford) 2011;50:926–31.

Recommendation 8:

- The separation of the second part of previous recommendation 8 ('when poor prognostic factors are present, addition of a bDMARD should be considered') and the new item 7 reflect the Task Force's desire to give stratification by prognostic factors more prominence.
- This recommendation was also expanded to include tsDMARDs, namely the Jak-inhibitor tofacitinib and further Jak-inhibitors, such as baricitinib. In the 2013 update, tsDMARDs (then recommendation 11) were recommended for use after a bDMARD had failed. Since then, more data on tofacitinib, especially regarding long-term safety aspects, and new data for baricitinib have been published. The data suggest that baricitinib may be more efficacious than a TNF-inhibitor.[154]

154 Taylor PC, Keystone EC, van der Heijde D, et al. Baricitinib versus placebo or adalimumab in patients with active rheumatoid arthritis (RA) and an inadequate response to background methotrexate therapy: results of a phase 3 study [Abstract]. Arthritis Rheum 2015;67(Suppl 10):L2.

Recommendation 9:

- This recommendation replaces former no. 9
- Compared with the 2013 update, more evidence has now accrued in favour of combination, even for tocilizumab.[167–169]
- Also for baricitinib, combination therapy conveys better structural, although not clinical or functional efficacy than monotherapy.[170]
- However, regarding signs and symptoms, physical function and joint damage, there are indications for a somewhat better efficacy of tocilizumab monotherapy, and more strongly so for Jak-inhibitors compared with MTX.[170–172]
- Monotherapy of the other biological agents has not been found clinically superior to MTX monotherapy.[66 67 173]
- Moreover, biologics can also be effectively combined with other csDMARDs.[142 144]

66 Klareskog L, van der Heijde D, de Jager JP, 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.
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167 Burmester GR, Rigby WF, van Vollenhoven RF, et al. Tocilizumab in early progressive rheumatoid arthritis: FUNCTION, a randomised controlled trial. Ann Rheum Dis 2016;75:1081–91.
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169 Dougados M, Kissel K, Conaghan PG, et al. Clinical, radiographic and immunogenic effects after 1 year of tocilizumab-based treatment strategies in rheumatoid arthritis: the ACT-RAY study. Ann Rheum Dis 2014;73: 803–9.
170 Fleischmann R, Takeuchi T, Schlichting D, et al. Baricitinib, methotrexate, or baricitinib plus methotrexate in patients with early rheumatoid arthritis who had received limited or no treatment with disease-modifying anti-rheumatic drugs (DMARDs): phase 3 trial results [abstract]. Arhritis Rheum 2015;67(Suppl 10). http://acrabstracts.org/abstract/baricitinib-methotrexate-or-baricitinib-plus-methotrexate-inpatients-with-early-rheumatoid-arthritis-who-had-received-limited-or-no-treatmentwith-disease-modifying-anti-rheumatic-drugs-dmards-p/ (accessed 4 Jan 2016).
171 Lee EB, Fleischmann RM, Hall S, et al. Radiographic, clinical and functional comparison of tofacitinib monotherapy versus methotrexate in methotrexate-nave patients with rheumatoid arthritis. Arthritis Rheum 2012;64:S1049.
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173 Emery P, Burmester GR, Bykerk VP, et al. Evaluating drug-free remission with abatacept in early rheumatoid arthritis: results from the phase 3b, multicentre, randomised, active-controlled AVERT study of 24 months, with a 12-month, double-blind treatment period. Ann Rheum Dis 2015;74:19–26.

Recommendation 10:

- The addition in the first part (‘or tsDMARD’) was partly needed because tsDMARDs (Jak inhibition) are now included in the earlier recommendations 8 and 9
- ‘First’ was deleted, because the Task Force did not decide to distinguish between failure of one or more bDMARDs.
- However, it must be noted that it is currently neither known if a Jak-inhibitor is effective once another one has failed nor established that a second IL-6 receptor inhibitor or inhibitors of the IL-6 ligand are effective if tocilizumab has failed

Recommendation 11:

- This item remained unchanged compared with the 2013 publication.
- No new data have been published that contest this conclusion.

Recommendation 12:

- No new evidence for or against this view has been found over the last years
- It was felt by the Task Force that mentioning the shared decision for this item among all 12 would imply that the other recommendations may not need to involve the patient

Sonstige Hinweise

Treatment flow chart in appendix (Figure 5).

García-Vicuna R et al., 2017 [9].

Spanish Rheumatology Society

Recommendations by the Spanish Rheumatology Society for the Management of Patients Diagnosed With Rheumatoid Arthritis who Cannot Be Treated With Methotrexate

Leitlinienorganisation/Fragestellung

The objective of the present report is to outline recommendations based on scientific evidence, and on the opinion of experts, for the management of patients with RA who cannot receive MTX because of contraindication, toxicity or lack of adherence to the drug regimen, and to establish efficient and safe therapeutic strategies that contribute to achieving a better control of the disease and quality care in these patients.

Methodik

Grundlage der Leitlinie

- Leitliniengremium bestehend aus 17 Rheumatologen, Teilnahme von Patientenvertretern nicht beschrieben
- Interessenkonflikte dargelegt, Umgang mit Interessenskonflikten im Konsensusprozess unklar;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formaler Konsensusprozess (Delphi-Methodik) zur Entwicklung der Leitlinienempfehlungen beim Vorliegen von wenig Evidenz (SIGN < 2++), bei Vorliegen von höherwertiger Evidenz kein Konsensusprozess
- kein externes Begutachtungsverfahren dargelegt
- Empfehlungen der Leitlinie sind eindeutig
- die Verbindung der Empfehlung mit der zugrundeliegenden Evidenz ist in Form einer Diskussion dargestellt
- Maßnahmen zur Überprüfung der Aktualität werden nicht beschrieben

Recherche/Suchzeitraum:

- searched for literature in the MEDLINE (PubMed)(1950–2015), EMBASE (1980–2015) and Cochrane Library (up to2015) databases

LoE / GoR

- according to SIGN (Figure 6)

Empfehlung bezüglich Therapie

Recommendations From the Spanish Society of Rheumatology for the Management of Patients With Rheumatoid Arthritis who Cannot Take Methotrexate.

	GR	LE	LA ≥ 4 (%)[a]
Therapeutic strategies			
R17. Patients with active RA who cannot take MTX due to a contraindication, toxicity or intolerance, can utilize other conventional DMARD, such as SSZ, or especially, LFN	D	4	100
R18. In patients with active RA in whom there is a contraindication, intolerance or circumstances that advise against the utilization of MTX, a biological treatment can be used as monotherapy. In this case, TCZ may be considered a preferable choice	B	1+	–

DMARD, disease-modifying antirheumatic drugs; GCP, good clinical practice; GR, grade of recommendation; LA, level of agreement; LE, level of evidence; LFN, leflunomide; MTX, methotrexate; RA, rheumatoid arthritis; SSZ, sulfasalazine; TCZ, tocilizumab.

[a] Level of agreement is shown only for the recommendations for which consensus was reached by a Delphi-like process.

Hintergrund R17:

Evidence summary. Leflunomide, above all, or SSZ can be comparable to MTX in efficacy.

Given the absence of articles to include after the selection ofreports retrieved from the literature search and taking, as a reference, the recommendations of the SER on biological therapies inpatients with RA,[59] which concludes that LFN, in particular, or SSZ can be comparable to MTX in efficacy, the authors of the present study have decided that it be a part of the body of evidence for drafting these recommendations.

Hintergrund R18:

Evidence summary. Monotherapy with TCZ is more effective than monotherapy with MTX. Alone, TCZ tends to achieve better responses than ADL monotherapy. In monotherapy, TCZ has responses similar to combined TCZ + MTX therapy, unlike anti-tumor necrosis factor ¸(anti-TNF¸) agents, which always have a better response when combined with MTX.

The use of TCZ as monotherapy is more effective than treatment as monotherapy with MTX/another synthetic DMARD (including SSZ, bucillamine and d-penicillamine).[73,74]

In contrast to what occurs with anti-TNFα agents,[78] the combined use of TCZ with MTX is not always superior to TCZ as monotherapy, in RA patients with an inadequate response to MTX.[74,79–81]

There are studies that analyze treatment with TNFα antagonists as monotherapy. With respect to ADL, it has been used as monotherapy and, in different dosing regimens, is superior to placebo in patients with RA and an inadequate response toDMARD.[88] Treatment with ADL as monotherapy has been seen to have the same clinical efficacy as treatment with MTX, although it is associated with a greater effect on arresting the radiological damage.[89] Patients with a low disease activity at the end of clinical trials in which they received ADL as monotherapy remained in the open-label extension after 6 years of good control of the disease and a minimal radiological progression.[89] Nevertheless, in both recent onset and established RA with an inadequate response to DMARD, in general, ADL as monotherapy is less efficacious. The most effective combination is ADL with MTX,[61] followed by ADL in combination with antimalarial agents and, finally, ADL plus LFN.[90]

Studies that analyze treatment with ETN as monotherapy demonstrate similar results. In the Early Rheumatoid Arthritis(ERA) study, which involved patients who had been diagnosed lessthan 3 years earlier and were MTX-naïve, it was observed that treatment with ETN as monotherapy had advantages in arresting the radiological damage; subcutaneous ETN monotherapy with 25 mg (twice a week), is significantly superior to MTX in controlling the signs and symptoms of RA, but only after 2 years offollow-up.[37,91] The RCT TEMPO[92] included patients with a mean disease duration of 6 years. Although some clinical and radiological scores showed a more favorable course with monotherapy with ETN rather than MTX, the most effective therapeutic arm was that which combined ETN with MTX, clearly superior to ETN as monotherapy.[93] In the open-label ADORE study,[94] after 16 weeks of treatment, it was observed that the effect of ETN as monotherapy was very similar to the effect of the combination of ETN plus MTX. The open- label RADIUS II observational registry also observed a similar response intreatment with ETN as monotherapy and combined ETN and MTXtherapy, evaluated using the Clinical Disease Activity Index (CDAI) to assess remission.[95]

... Patients with RA who receive monotherapy consisting of INF have a shorter drug survival and more adverse events than patients who take INF in combination with MTX.[78,98] Monotherapy with certolizumab pegol was superior to placebo in the FAST4WARD study,[99] and similar to con-comitant treatment with DMARD in the REALISTIC,[82] regardless of the anti-TNFα used previously. Monotherapy with other biological agents that do not inhibit TNFα, aside from TCZ, has not been thoroughly researched, although there are a few studies that evaluate the clinical efficacy of treatment with ABT (ARRIVE) and RTX as monotherapy.[100]

Available data[74,101,102] indicate that treatment with anti-TNFα, agents, ABT and TCZ utilized in combination with MTX have responses that are comparable (through comparisons, mostly indi-rect) in RA patients and an inadequate response to DMARD. However, administered as monotherapy, TCZ is associated with a better clinical response than anti-TNFα drugs.[102,103] The responses in terms of efficacy are similar in TCZ associated with MTX and TCZ as monotherapy, whereas, anti-TNFα agents combined with MTX generally show a greater therapeutic efficacy than anti-TNFα monotherapy. These findings suggest that treatment with TCZ as monotherapy [73,85,104] should be considered an effective therapeutic alternative in patients with active RA that is refractory to MTX, who should receive a biological agent but do not tolerate MTX or do not adhere to a treatment that includes it.

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Singh JA et al., 2016 [28].

2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis

Fragestellung:

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:

- Leitliniengremium aus Rheumatologen und 2 Patientenvertretern
- Interessenkonflikte dargelegt, Umgang mit Interessenskonflikten im Konsensusprozess unklar;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse (70% consensus threshold) und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Überprüfung der Aktualität wird nicht beschrieben

Recherche/Suchzeitraum:

- Systematic literature search in OVID Medline, Embase, and the Cochrane Library until Sept 2014

LoE / GoR

- Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology
- quality of evidence for each outcome could be rated as high, moderate, low, or very low

	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.

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.

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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.
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- *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.

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- *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.
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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.

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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.
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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.

For all scenarios for established RA below, treatment may be with or without MTX.

- **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.
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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.
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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.
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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)

Sonstige Hinweise

Treatment flow chart in appendix (Figures 2 & 3)

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 5 of 12, May 2019) am 07.05.2019

#	Suchfrage
1	[mh “Arthritis, Rheumatoid”]
2	(rheumatoid AND arthrit*):ti,ab,kw
3	(OR #1-#2)
4	#3 with Cochrane Library publication date from May 2014 to present

Systematic Reviews in Medline (PubMed) am 07.05.2019

#	Suchfrage
1	"arthritis, rheumatoid/therapy"[mh]
2	rheumatoid[tiab] AND arthrit*[tiab]
3	(((sjogren*[tiab] OR sjögren*[tiab] OR sicca*[tiab]) OR caplan*[tiab] OR felty*[tiab]) AND syndrom*[tiab]) OR (rheumatoid[tiab] AND vasculiti*[tiab]) OR (still*[tiab] AND disease[tiab] AND (adult-onset[tiab] OR (adult[tiab] AND onset[tiab])))
4	(treatment*[tiab] OR treating[tiab] OR treated[tiab] OR treat[tiab] OR treats[tiab] OR treatab*[tiab] OR therapy[tiab] OR therapies[tiab] OR therapeutic*[tiab] OR monotherap*[tiab] OR polytherap*[tiab] OR pharmacotherap*[tiab] OR effect*[tiab] OR efficacy[tiab] OR management[tiab] OR drug*[tiab])
5	#1 OR ((#2 OR #3) AND #4)
6	(#5) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis [pt] OR meta-analysis [ti] OR systematic literature review [ti] OR this systematic review [tw] OR pooling project [tw] OR (systematic review [tiab] AND review [pt]) OR meta synthesis [ti] OR meta-analy*[ti] OR integrative review [tw] OR integrative research review [tw] OR rapid review [tw] OR umbrella review [tw] OR consensus development conference [pt] OR practice guideline [pt] OR drug class reviews [ti] OR cochrane database syst rev [ta] OR acp journal club [ta] OR health technol assess [ta] OR evid rep technol assess summ [ta] OR jbi database system rev implement rep [ta]) OR (clinical guideline [tw] AND management [tw]) OR ((evidence based[ti] OR evidence-based medicine [mh] OR best practice* [ti] OR evidence synthesis [tiab]) AND (review [pt] OR diseases category[mh] OR behavior and behavior mechanisms [mh] OR therapeutics [mh] OR evaluation studies[pt] OR validation studies[pt] OR guideline [pt] OR pmcbook)) OR ((systematic [tw] OR systematically [tw] OR critical [tiab] OR (study selection [tw]) OR (predetermined [tw] OR inclusion [tw] AND criteri* [tw]) OR exclusion criteri* [tw] OR main outcome measures [tw] OR standard of care [tw] OR standards of care [tw]) AND (survey [tiab] OR surveys [tiab] OR overview* [tw] OR review [tiab] OR reviews [tiab] OR search* [tw] OR handsearch [tw] OR analysis [ti] OR critique [tiab] OR appraisal [tw] OR (reduction [tw]AND (risk [mh] OR risk [tw]) AND (death OR recurrence))) AND (literature [tiab] OR articles [tiab] OR publications [tiab] OR publication [tiab] OR bibliography [tiab] OR bibliographies [tiab] OR published [tiab] OR pooled data [tw] OR unpublished [tw] OR citation [tw] OR citations [tw] OR database [tiab] OR internet [tiab] OR textbooks [tiab] OR references [tw] OR scales [tw] OR papers [tw] OR datasets [tw] OR trials [tiab] OR meta-analy* [tw] OR (clinical [tiab] AND studies [tiab]) OR treatment outcome [mh] OR treatment outcome [tw] OR pmcbook)) NOT (letter [pt] OR newspaper article [pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab]

	OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
7	((#6) AND ("2014/05/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))

Leitlinien in Medline (PubMed) am 07.05.2019

#	**Suchfrage**
1	"arthritis, rheumatoid"[mh]
2	((rheumatoid[tiab] AND arthrit*[tiab])) OR ((((sjogren*[tiab] OR sjögren*[tiab] OR sicca*[tiab]) OR caplan*[tiab] OR felty*[tiab]) AND syndrom*[tiab]) OR (rheumatoid[tiab] AND vasculiti*[tiab]) OR (still*[tiab] AND disease[tiab] AND (adult-onset[tiab] OR (adult[tiab] AND onset[tiab]))))
3	#1 OR #2
4	(#3) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR recommendation*[ti])*
5	(((#4) AND ("2014/05/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp]))

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2. **Bae SC, Lee YH.** Comparison of the efficacy and safety of tofacitinib and baricitinib in patients with active rheumatoid arthritis: a Bayesian network meta-analysis of randomized controlled trials. Z Rheumatol 06.09.2018 [Epub ahead of print].

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8. **Fiehn C, Holle J, Iking-Konert C, Leipe J, Weseloh C, Frerix M, et al.** Therapie der rheumatoiden Arthritis mit krankheitsmodifizierenden Medikamenten; S2e-Leitlinie; Leitlinienreport [online]. AWMF-Registernummer 060-004. Berlin (GER): Arbeitsgemeinschaft der Wissenschaftlichen Medizinschen Fachgesellschaften (AWMF); 2018. [Zugriff: 07.05.2019]. URL: https://www.awmf.org/uploads/tx_szleitlinien/060-004m_S2e_Therapie_rheumatoide_Arthritits_krankheitsmod_Med_2018-10.pdf.

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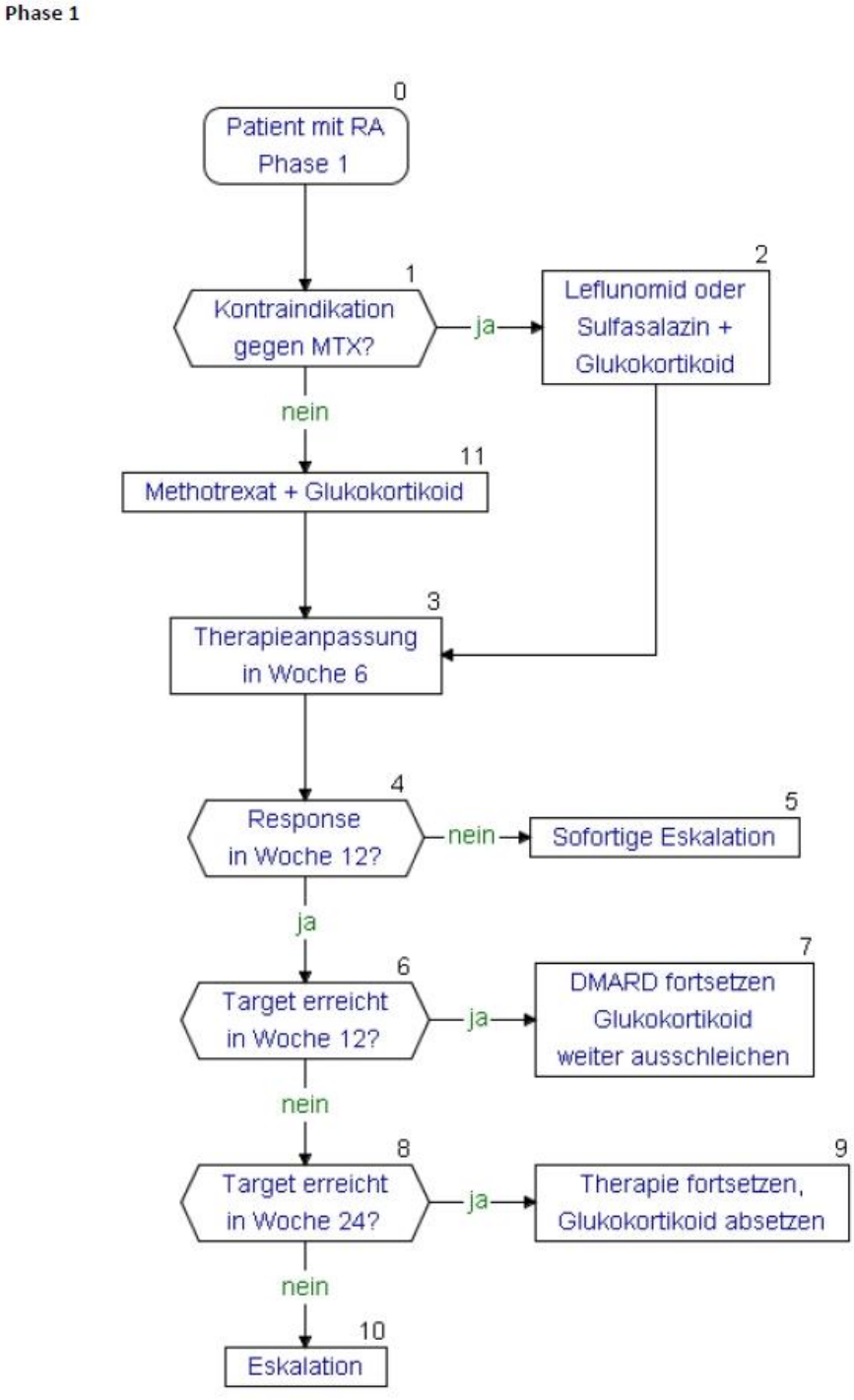
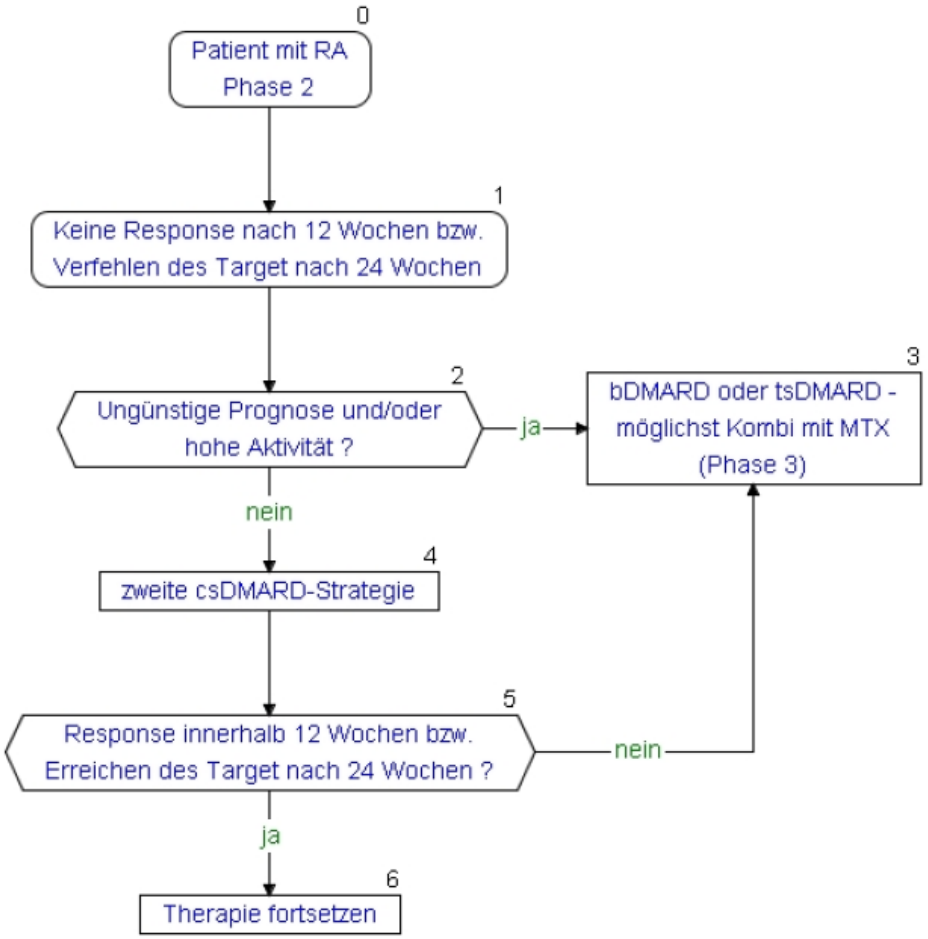
Anhang

Figure 1: *Therapiealgorithmus für die Behandlung der RA mit krankheitsmodifizierenden Medikamenten (Definitionen siehe Glossar). Therapieanpassung in Woche 6 (Phase 1, Schritt 3) bedeutet die Optimierung der Therapie durch Anpassung der Dosierungen der Medikamente und ggf. dem Wechsel der Applikationsform (s.c. statt p.o.). Zu diesem Zeitpunkt sollten auch die Verträglichkeit der Medikation und die Adhärenz des Patienten an die Medikation überprüft werden (siehe auch Empfehlung Nr. 7) [7]*



Phase 2



Phase 3

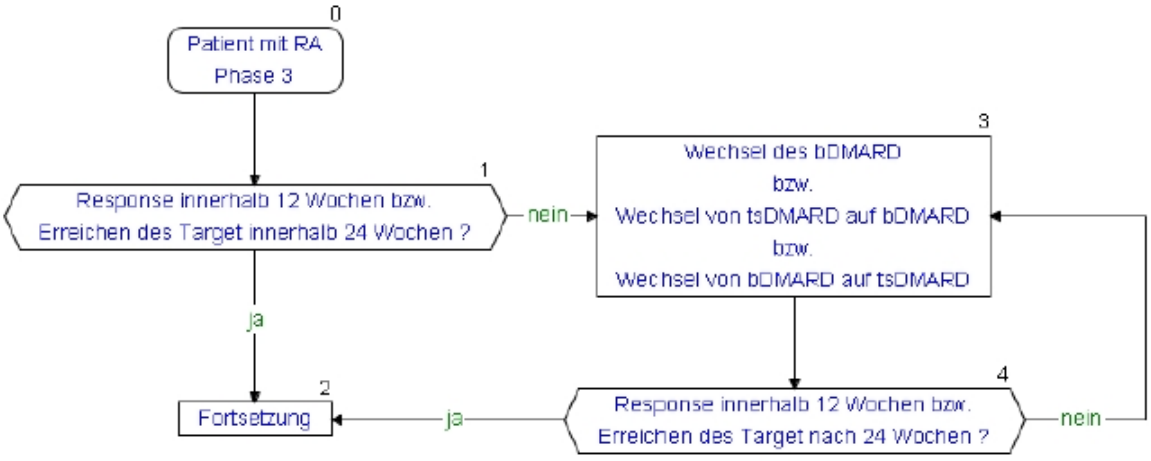


Figure 2: *2015 American College of Rheumatology (ACR) recommendations for the treatment of Early RA, defined as disease duration ,6 months. *5consider adding low-dose glucocorticoids (#10 mg/day of prednisone or equivalent) in patients with moderate or high RA disease activity when starting disease-modifying antirheumatic drugs (DMARDs) and in patients with DMARD failure or biologic failure. †5also consider using short-term glucocorticoids (defined as ,3 months treatment) for RA disease flares. Glucocorticoids should be used at the lowest possible dose and for the shortest possible duration to provide the best benefit-risk ratio for the patient. #5treatment target should ideally be low disease activity or remission. For the level of evidence supporting each recommendation, see the related section in the Results. This figure is derived from recommendations based on PICO (population, intervention, comparator, and outcomes) questions A.1 to A.12. [28]*

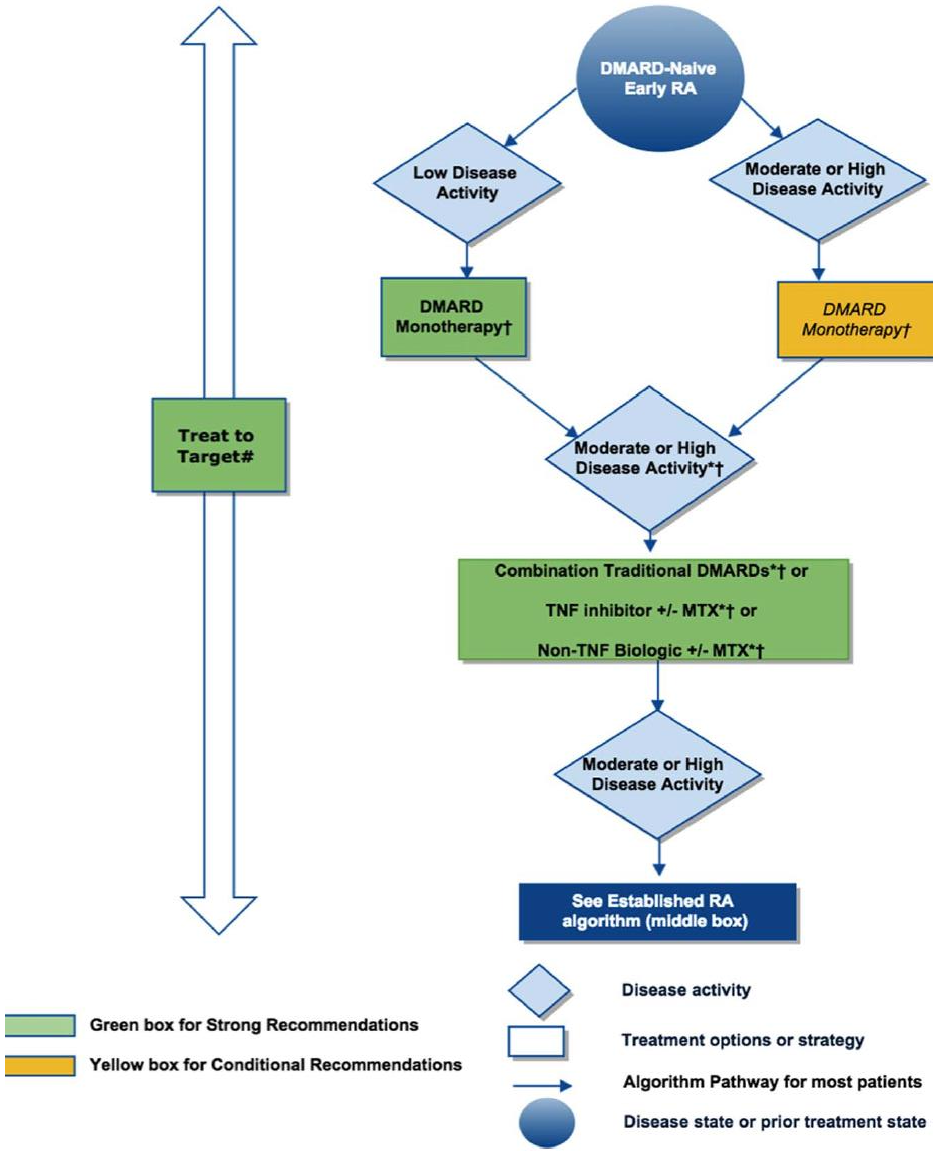


Figure 3: *2015 ACR recommendations for the treatment of Established RA, defined as disease duration $6 months, or meeting the 1987 ACR classification criteria (81). Due to complexity of management of established RA, not all clinical situations and choices could be depicted in this flow chart, and therefore we show the key recommendations. For a complete list of recommendations, please refer to the Results. * 5 consider adding low-dose glucocorticoids (#10 mg/day of prednisone or equivalent) in patients with moderate or high RA disease activity when starting traditional disease-modifying antirheumatic drugs (DMARDs) and in patients with DMARD failure or biologic failure. †5also consider using short-term glucocorticoids (defined as ,3 months treatment) for RA disease flares. Glucocorticoids should be used at the lowest possible dose and for the shortest possible duration to provide the best benefit-risk ratio for the patient. #5treatment target should ideally be low disease activity or remission. **5tapering denotes scaling back therapy (reducing dose or dosing frequency), not discontinuing it and if done, must be conducted slowly and carefully. For the level of evidence supporting each recommendation, see the related section in the Results. This figure is derived from recommendations based on PICO (population, intervention, comparator, and outcomes) questions B.1 to B.38. [28]*

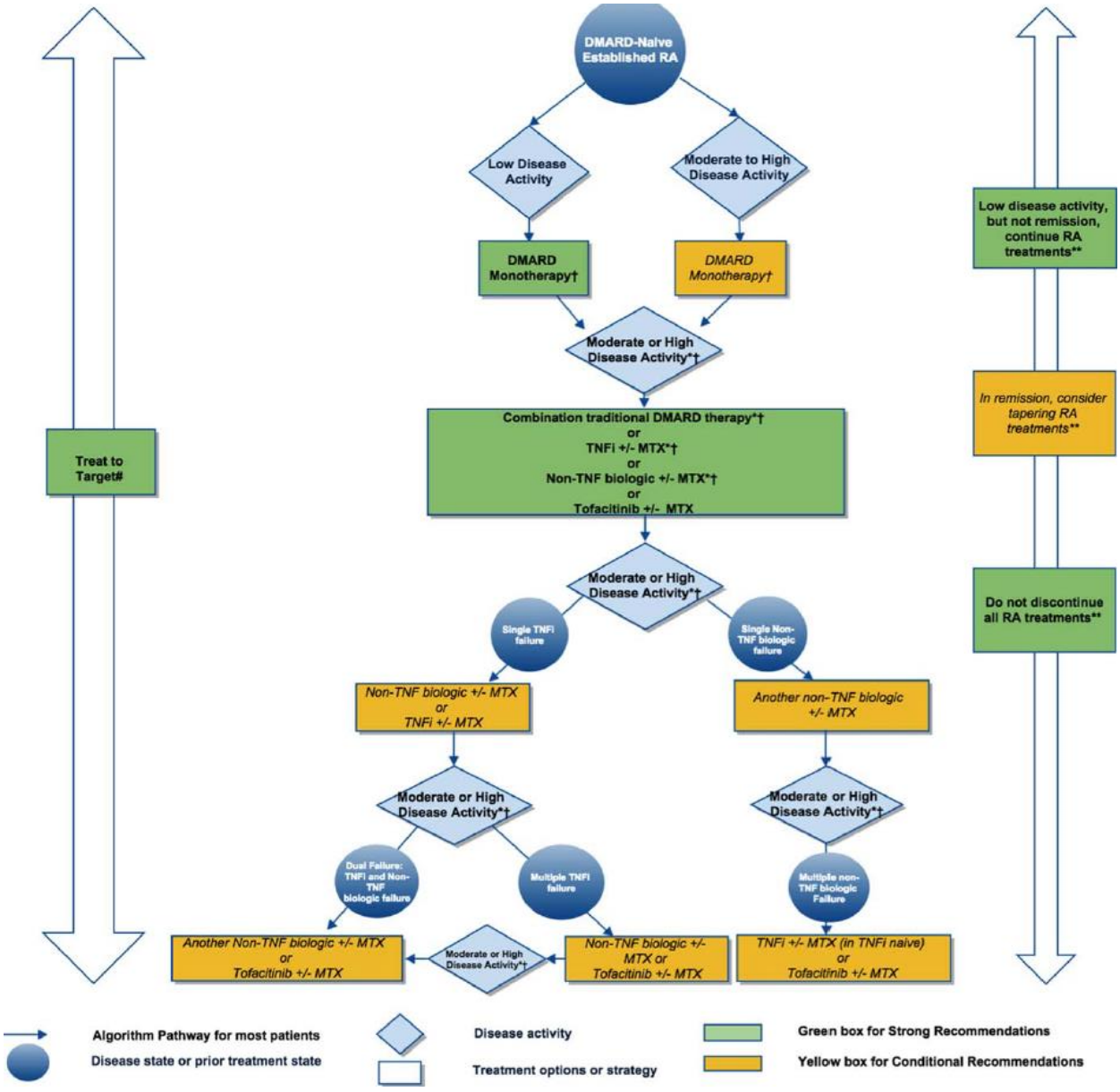


Figure 4: Strategy for the pharmacological treatment of rheumatoid arthritis (RA) [6]

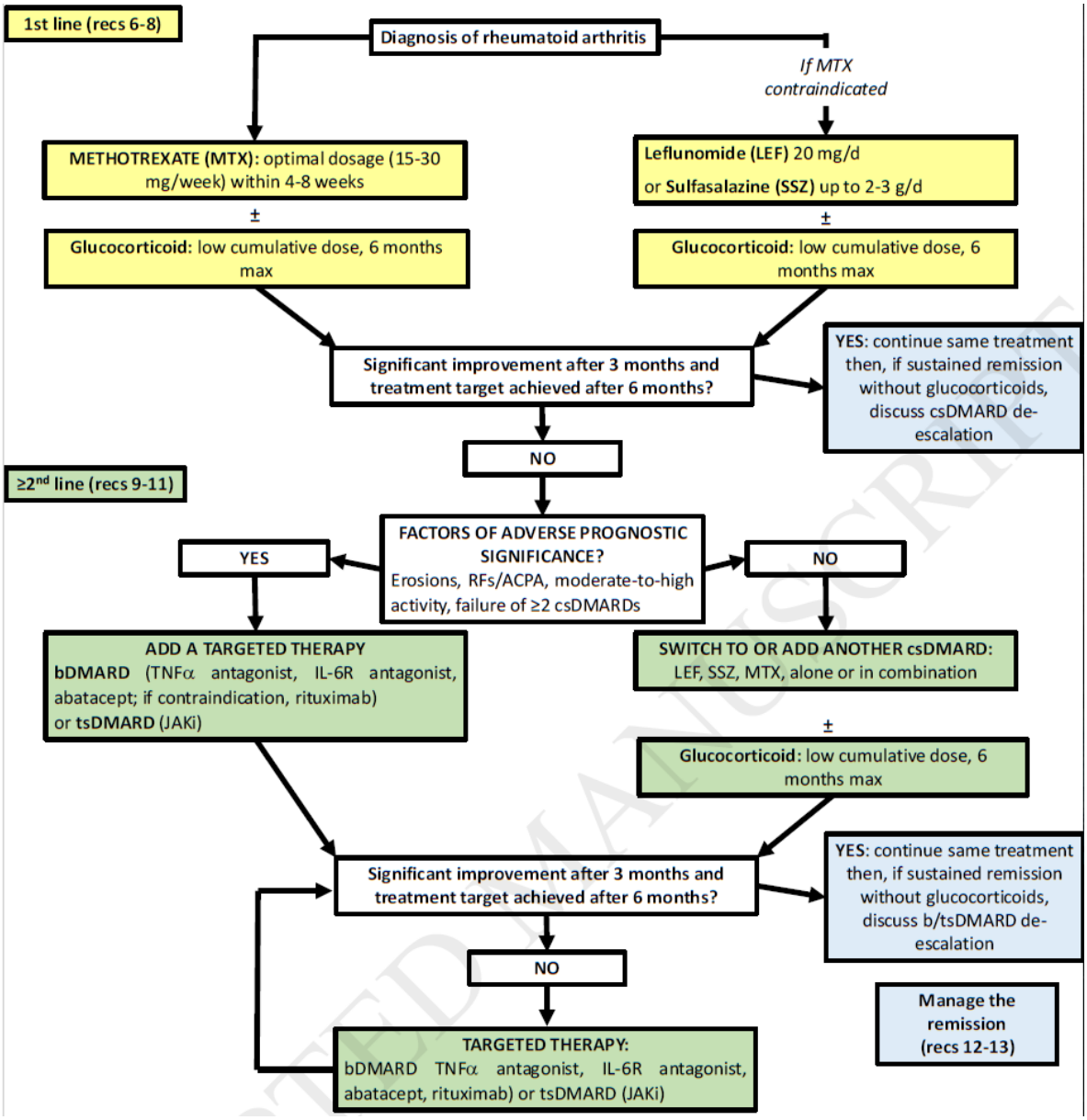
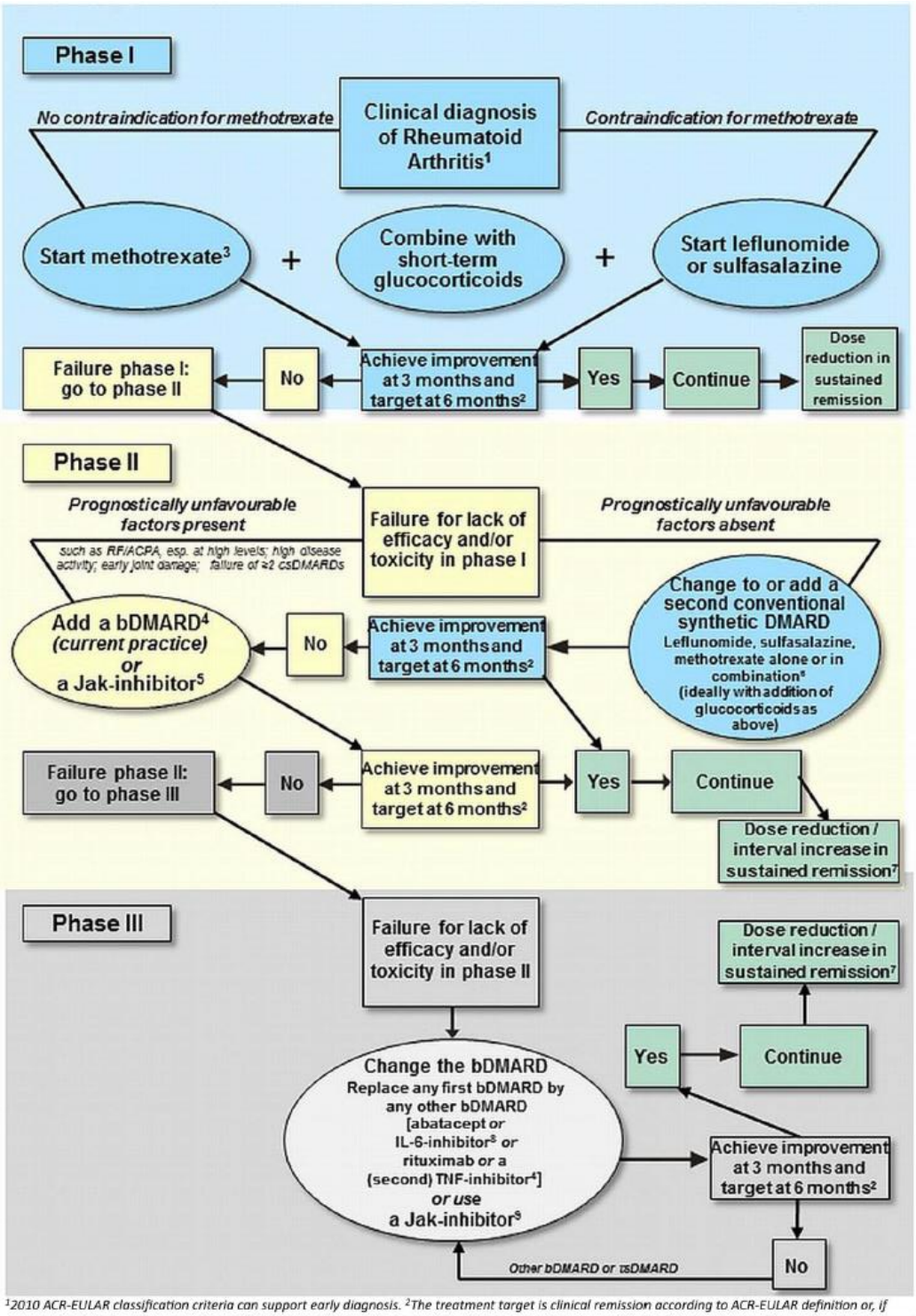


Figure 5: Algorithm based on the 2016 European League Against Rheumatism (EULAR) recommendations on rheumatoid arthritis (RA) management [29]



[1]2010 ACR-EULAR classification criteria can support early diagnosis. [2]The treatment target is clinical remission according to ACR-EULAR definition or, if remission is unlikely to be achievable, at least low disease activity; the target should be reached after 6 months, but therapy should be adapted or changed if no sufficient improvement is seen after 3 months. [3]"Methotrexate should be part of the first treatment strategy"; while combination therapy of csDMARDs is not preferred by the Task Force, starting with methotrexate does not exclude its use in combination with other csDMARDs. [4]TNF-inhibitors (adalimumab, certolizumab, etanercept, golimumab, infliximab, including EMA/FDA approved bsDMARDs), abatacept, IL-6-inhibitors, or rituximab; in patients who cannot use csDMARDs as comedication, IL6-inhibitors and tsDMARDs have some advantages. [5]Current practice would be to start with a bDMARD (in combination with MTX or another csDMARD) because of the long-term experience compared with tsDMARDs (Jak-inhibitors). [6]The most frequently used combination comprises methotrexate, sulfasalazine and hydroxychloroquine. [7]Dose reduction or interval increase can be safely done with all bDMARDs with little risk of flares; stopping is associated with high flare rates; most but not all patients can recapture their good state upon re-institution of the same bDMARD. [8]Efficacy and safety of bDMARDs after Jak-inhibitor failure is unknown; also, efficacy and safety of an IL-6 pathway inhibitor after another one has failed is currently unknown. [9]Efficacy and safety of a Jak-inhibitor after insufficient response to a previous Jak-inhibitor is unknown.

Figure 6: Levels of Evidence and Grades of recommendation according to SIGN (1999-2012)

Levels of evidence

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

Grades of recommendations

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; orExtrapolated 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+