

# **Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie**

**und**

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

**Vorgang: 2020-B-023 Ozanimod**

Stand: April 2020

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

### Ozanimod zur Behandlung der RRMS

#### 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 Übersicht "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	<p><u>Nutzenbewertungsbeschlüsse nach § 35a SGB V</u></p> <ul style="list-style-type: none"><li>- Fampridin: Beschluss nach § 35a SGB V vom 2. August 2012</li><li>- Teriflunomod: Beschluss nach § 35a SGB V vom 20. März 2014</li><li>- Dimethylfumarat: Beschluss nach § 35a SGB V vom 16. Oktober 2014</li><li>- Fingolimod: Beschluss nach § 35a SGB V vom 1. Oktober 2015 (Neubewertung nach Fristablauf), 19. Mai 2016 (neues Anwendungsgebiet), 20. Juni 2019 (neues Anwendungsgebiet)</li><li>- Cladribin: Beschluss nach § 35a SGB V vom 17. Mai 2018</li><li>- Ocrelizumab: Beschluss nach § 35a SGB V vom 2. August 2018</li><li>- Extrakt aus Cannabis Sativa: Beschluss nach § 35a SGB V vom 1. November 2018 (Neubewertung nach Fristablauf)</li></ul> <p><u>Therapiehinweise zu Arzneimittelanwendungen</u></p> <p>Alemtuzumab: Arzneimittelrichtlinie Anlage IV; Therapiehinweis vom 15. September 2016 Natalizumab: Arzneimittelrichtlinie Anlage IV; Therapiehinweis vom 16. Oktober 2009</p>
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

<b>Wirkstoff ATC-Code Handelsname</b>	<b>Anwendungsgebiet (Text aus Fachinformation)</b>
Zu bewertendes Arzneimittel:	
Ozanimod L04AA38 Zeposia®	Behandlung von erwachsenen Patienten mit schubförmig remittierender Multipler Sklerose (RRMS) mit aktiver Erkrankung definiert durch klinischen Befund oder Bildgebung.
Interferon beta-1a, L03AB07 Avonex®	<p>AVONEX ist indiziert für die Behandlung von</p> <ul style="list-style-type: none"> <li>– Patienten mit schubförmiger Multipler Sklerose (MS). In klinischen Studien war diese durch mindestens zwei akut auftretende Exazerbationen (Schübe) während der letzten drei Jahre gekennzeichnet ohne Hinweise auf ein kontinuierliches Fortschreiten der Erkrankung zwischen den Schüben. AVONEX verlangsamt das Fortschreiten der Behinderung und verringert die Häufigkeit von Schüben.</li> <li>– Patienten nach einem einmaligen demyelinisierenden Ereignis mit aktivem, entzündlichen Prozess, wenn dieses demyelinisierende Ereignis eine intravenöse Kortikosteroidtherapie rechtfertigt, alternative Diagnosen ausgeschlossen wurden und ein hohes Risiko für die Entwicklung einer klinisch gesicherten Multiplen Sklerose besteht (siehe Abschnitt 5.1).</li> </ul> <p>AVONEX ist bei Patienten, die eine progrediente Form der MS entwickeln, abzusetzen.</p> <p>(FI Stand: September 2019)</p>
Rebif®	<p>Rebif wird angewendet zur Behandlung von Patienten mit schubförmiger Multipler Sklerose. In klinischen Studien wurde dies durch zwei oder mehr akute Schübe innerhalb der vorausgegangenen zwei Jahre charakterisiert (siehe Abschnitt 5.1).</p> <p>Bei Patienten mit sekundär progredienter Multipler Sklerose ohne vorhandene Schubaktivität konnte eine Wirksamkeit nicht nachgewiesen werden (siehe Abschnitt 5.1).</p> <p>(FI Stand: Januar 2020)</p>
Interferon beta-1b L03AB08 Betaferon®, Extavia®	<p>Betaferon wird angewendet zur Behandlung von</p> <ul style="list-style-type: none"> <li>- Patienten mit erstmaligem demyelinisierendem Ereignis mit aktivem entzündlichem Prozess, wenn dieses Ereignis schwer genug ist, um eine intravenöse Kortikosteroidtherapie zu rechtfertigen, wenn mögliche Differentialdiagnosen ausgeschlossen wurden und wenn bei diesen Patienten der Beurteilung zufolge ein hohes Risiko für das Auftreten einer klinisch gesicherten Multiplen Sklerose besteht (siehe Abschnitt 5.1).</li> <li>- Patienten mit schubweise verlaufender Multipler Sklerose, die in den letzten zwei Jahren zwei oder mehr Schübe durchgemacht haben.</li> <li>- Patienten mit sekundär progredient verlaufender Multipler Sklerose, die sich in einem akuten Krankheitsstadium befinden, d.h. klinische Schübe erfahren.</li> </ul> <p>(FI Stand: September 2019)</p>

## II. Zugelassene Arzneimittel im Anwendungsgebiet

Peginterferon beta-1a L03AB13 Plegridy®	Plegridy wird angewendet zur Behandlung von erwachsenen Patienten mit schubförmig remittierender Multipler Sklerose (siehe Abschnitt 5.1). (FI Stand: September 2019)
Glucocorticoide: Methylprednisolon H02AB04 Generika;  Prednisolon H02AB06 Generika	Methylprednisolon acis kann weiterhin zur kurzfristigen Behandlung von akuten Schüben bei multipler Sklerose angewendet werden. Methylprednisolon acis kann die Schubdauer verkürzen, hat jedoch keinen Einfluss auf die Schubrate oder auf die Behinderungsprogression.  Multiple Sklerose (zum oralen Ausschleichen nach hochdosierter parenteraler Glucocorticoidgabe im Rahmen eines akuten Schubes)
Alemtuzumab L04AA34 LEMTRADA®	LEMTRADA ist angezeigt für die krankheitsmodifizierende Monotherapie bei Erwachsenen mit hochaktiver schubförmig-remittierender Multipler Sklerose (relapsing remitting multiple sclerosis, RRMS) bei folgenden Patientengruppen: <ul style="list-style-type: none"> <li>- Patienten mit hochaktiver Erkrankung trotz vollständiger und angemessener Behandlung mit mindestens einer rankheitsmodifizierenden Therapie (disease modifying therapy, DMT)</li> <li>- Patienten mit rasch fortschreitender schwerer schubförmig-remittierender Multipler Sklerose, definiert durch 2 oder mehr Schübe mit Behinderungsprogression in einem Jahr, und mit einer oder mehr Gadolinium-anreichernden Läsionen in der MRT des Gehirns oder mit einer signifikanten Erhöhung der T2-Läsionen im Vergleich zu einer kürzlich durchgeföhrten MRT.</li> </ul> (FI Stand: Januar 2020)
Azathioprin L04AX01 Imurek®/Generika	Azathioprin ist angezeigt bei schubförmiger Multipler Sklerose, wenn eine immunmodulatorische Therapie angezeigt und eine Therapie mit Beta-Interferonen nicht möglich ist, oder unter einer bisherigen Therapie mit Azathioprin ein stabiler Verlauf erreicht wurde.
Cladribin L01BB04 MAVENCLAD	MAVENCLAD wird angewendet zur Behandlung von erwachsenen Patienten mit hochaktiver schubförmiger Multipler Sklerose (MS), definiert durch klinische oder bildgebende Befunde (siehe Abschnitt 5.1).
Dimethylfumarat N07XX09 Tecfidera®	Tecfidera wird zur Behandlung von erwachsenen Patienten mit schubförmig remittierender Multipler Sklerose angewendet (siehe Abschnitt 5.1 für wichtige Informationen über die Populationen, für die eine Wirksamkeit bestätigt wurde). (FI Stand: Januar 2020)

## II. Zugelassene Arzneimittel im Anwendungsgebiet

Fingolimod L04AA27 Gilenya®	<p>Gilenya ist als krankheitsmodifizierende Monotherapie von hochaktiver schubförmig-remittierend verlaufender Multipler Sklerose bei folgenden Gruppen erwachsener Patienten und Kindern und Jugendlichen ab einem Alter von 10 Jahren angezeigt:</p> <ul style="list-style-type: none"> <li>– Patienten mit hochaktiver Erkrankung trotz Behandlung mit einem vollständigen und angemessenen Zyklus mit mindestens einer krankheitsmodifizierenden Therapie (Ausnahmen und Informationen zu Auswaschphasen siehe Abschnitte 4.4 und 5.1).</li> </ul> <p>oder</p> <ul style="list-style-type: none"> <li>– Patienten mit rasch fortschreitender schwerer schubförmig-remittierend verlaufender Multipler Sklerose, definiert durch zwei oder mehr Schübe mit Behinderungsprogression in einem Jahr, und mit einer oder mehr Gadolinium anreichernden Läsionen im MRT des Gehirns oder mit einer signifikanten Erhöhung der T2-Läsionen im Vergleich zu einer kürzlich durchgeföhrten MRT.</li> </ul> <p>(FI Stand: Dezember 2019)</p>
Glatirameracetat L03AX13 Glatirameracetat AbZ	<p>Glatirameracetat AbZ wird angewendet zur Behandlung der schubförmigen multiplen Sklerose (MS) (wichtige Informationen über die Patientengruppe, in der die Wirksamkeit belegt wurde, siehe Abschnitt 5.1).</p> <p>Glatirameracetat AbZ ist nicht indiziert bei primär oder sekundär progredienter MS.</p> <p>(FI Stand: September 2019)</p>
Mitoxantron L01DB07 Ralenova®	<p>Mitoxantron ist indiziert zur Behandlung von Patienten mit hochaktiver schubförmiger multipler Sklerose verbunden mit sich rasch entwickelnder Behinderung, für die keine alternativen Therapieoptionen bestehen (siehe Abschnitte 4.2, 4.4 und 5.1).</p> <p>(FI Stand: Oktober 2018)</p>
Natalizumab L04AA23 TYSABRI®	<p>TYSABRI wird angewendet für die krankheitsmodifizierende Monotherapie bei Erwachsenen mit hochaktiver, schubförmig remittierend verlaufender Multipler Sklerose (MS) bei folgenden Patientengruppen:</p> <ul style="list-style-type: none"> <li>- Patienten mit hochaktiver Erkrankung trotz Behandlung mit einem vollständigen und angemessenen Zyklus mit mindestens einer krankheitsmodifizierenden Therapie (DMT) (Ausnahmen und Informationen zu Auswaschphasen siehe Abschnitte 4.4 und 5.1).</li> <li>- Patienten mit rasch fortschreitender schubförmig remittierend verlaufender Multipler Sklerose, definiert durch 2 oder mehr Schübe mit Behinderungsprogression in einem Jahr, und mit 1 oder mehr Gadolinium-anreichernden Läsionen in der MRT des Gehirns oder mit einer signifikanten Erhöhung der T2-Läsionen im Vergleich zu einer kürzlich durchgeföhrten MRT.</li> </ul> <p>(FI Stand: Oktober 2019)</p>
Ocrelizumab L04AA36 Ocrevus®	<p>Ocrevus ist angezeigt zur Behandlung erwachsener Patienten mit schubförmiger Multipler Sklerose (RMS) mit aktiver Erkrankung, definiert durch klinischen Befund oder Bildgebung (siehe Abschnitt 5.1).</p> <p>Ocrevus ist angezeigt zur Behandlung erwachsener Patienten mit früher primär progredienter Multipler Sklerose (PPMS), charakterisiert anhand der Krankheitsdauer und dem Grad der Behinderung, sowie mit Bildgebungsmerkmalen, die typisch für eine Entzündungsaktivität sind (siehe Abschnitt 5.1).</p> <p>(FI Stand: Dezember 2019)</p>

## **II. Zugelassene Arzneimittel im Anwendungsgebiet**

Teriflunomid L04AA31 AUBAGIO®	AUBAGIO ist zur Behandlung erwachsener Patienten mit schubförmig-remittierender Multipler Sklerose (MS) angezeigt. Siehe Abschnitt 5.1 für weitere Informationen über die Patienten, bei denen die Wirksamkeit nachgewiesen wurde. (FI Stand: Oktober 2019)
Siponimod L04AA42 Mayzent®	Mayzent wird angewendet zur Behandlung von erwachsenen Patienten mit sekundär progredienter Multipler Sklerose (SPMS) mit Krankheitsaktivität, nachgewiesen durch Schübe oder Bildgebung der entzündlichen Aktivität (siehe Abschnitt 5.1).

Quellen: AMIS-Datenbank, Fachinformationen



## Abteilung Fachberatung Medizin

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

**Vorgang: 2020-B-023 (Ozanimod)**

Auftrag von: Abt. AM

Bearbeitet von: Abt. FB Med

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## Abkürzungsverzeichnis

AE	adverse events
ARR	Annualised relapse rate
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BID	Twice daily
CDP	confirmed disability progression
CIS	clinically isolated syndrome
Col	Conflict of interest
DAE	discontinuations due to adverse events
DIC	disability improvement confirmed
DMD	Disease modifying drug
DMF	dimethyl fumarate
DMT	Disease modifying therapy
DPC	disability progression confirmed
ECRI	ECRI Guidelines Trust
EDSS	Expanded Disability Status Scale
EOD	every other day
FGD	Fingolimod
GA	Glatiramer Acetate
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HA	highly active
HD	High Dose
HDA	high disease activity
HR	Hazard Ratio
HRA+DAT	high disease activity
IFN-β	Beta-Interferone
IM	Intramuscular
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
ITC	indirect treatment comparison
JCV	John Cunningham virus
KI	Konfidenzintervall
LD	Low Dose
LoE	Level of Evidence
mcg	Mikrogramm
MRI	magnetic resonance imaging
MS	Multiple Sclerosis
n.s.	Nicht signifikant

NEDA	no evidence of disability progression
NICE	National Institute for Health and Care Excellence
NMA	Netwerkmetaanalyse
NZT	Natalizumab
OR	Odds Ratio
PML	Progressive multifocal leukoencephalopathy
PRMS	progressive relapsing MS
RES	Rapidly evolving severe
RR	Relatives Risiko
RRMS	Schubförmig verlaufende MS („relapsing-remitting“, RRMS)
RTI	Respiratory tract infection
SAE	Serious AE
SC	Subcutaneous
SF-36	Short Form 36
SIGN	Scottish Intercollegiate Guidelines Network
SOT	sub-optimal therapy
SP	Secondary Progressive
SPMS	secondary progressive MS
TIW	three times a week
TRIP	Turn Research into Practice Database
WHO	World Health Organization

## 1 Indikation

Hochaktive schubförmig remittierende Multiple Sklerose (RRMS) und rasch fortschreitende schwere schubförmig-remittierend verlaufende MS.

## 2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation Multipler Sklerose durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 04.02.2020 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, ECRI, G-BA, GIN, 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.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Die Recherche ergab 898 Quellen. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 30 Quellen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

## 3 Ergebnisse

### 3.1 G-BA Beschlüsse

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#### G-BA, 2008 [4].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie in Anlage 4: Therapiehinweis zu Natalizumab vom 16. Oktober 2008

#### Fazit

- Für die Zulassung wurde die Wirksamkeit und Sicherheit von Natalizumab in zwei großen multizentrischen randomisierten kontrollierten doppelblinden Phase-III-Studien geprüft. In beiden Studien wurden Patienten mit schubförmig verlaufender MS aufgenommen, die mindestens einen Schub im Jahr zuvor erlebt hatten. Die Diagnose einer MS war nach den Kriterien von Mc Donald et al. gesichert. Im MRT lagen mit einer MS vereinbare radiologische Veränderungen vor. Weitere Einschlusskriterien waren ein Alter zwischen 18 und 55 Jahren und ein Score von 0 – 5 auf der „Expanded Disability Status Scale“ (EDSS). Ausschluss-kriterien waren eine immunsuppressive Therapie innerhalb der letzten sechs Monate, ein entzündlicher Schub oder Gabe von Glucosteroiden in den letzten 50 Tagen sowie eine primär oder sekundär progressive Verlaufsform der MS.
- Bei der AFFIRM-Studie (Polman et al.) handelte es sich um eine Natalizumab-Monotherapie-Studie mit Patienten, die innerhalb der letzten sechs Monate nicht mit Interferonen behandelt worden waren und auch insgesamt nicht länger als sechs Monate Interferone erhalten hatten. Die Patienten wurden im Verhältnis 2:1 randomisiert den Behandlungsarmen mit Natalizumab 300 mg (n = 627) bzw. Placebo (n = 315) alle vier Wochen zugewiesen.
- Primäre Endpunkte waren die Schubrate nach einem Jahr und die Progression der Behinderung nach zwei Jahren, definiert als eine für mindestens 12 Wochen anhaltende Erhöhung um mindestens 1,0 auf der EDSS bei einem Ausgangs-EDSS  $\geq 1,0$  oder eine Erhöhung um mindestens 1,5 auf der EDSS bei einem Ausgangs-EDSS = 0. Sekundäre Endpunkte waren der Anteil schubfreier Patienten sowie radiologische Veränderungen in der MRT.
- Nach einem Jahr reduzierte sich die Schubrate unter Natalizumab signifikant auf 0,26 gegenüber 0,81 unter Placebo entsprechend einer relativen Risikoreduktion um 68 %. Diese Verminderung der Schubrate setzte sich im zweiten Behandlungsjahr fort.
- Nach zwei Jahren sank das Risiko einer Progression der Behinderung signifikant um 12 %. Während es unter Placebo bei 29 % der Patienten zu einer Progression kam, waren es unter Natalizumab nur 17 %. Dies entspricht einer Number Needed to Treat (NNT) von 9 und einer relativen Risikoreduktion von 42 %.
- Der Anteil schubfreier Patienten betrug unter Placebo 41 % und unter Natalizumab 67 %. Unter Natalizumab zeigten im MRT 97 % der Patienten keine Gadolinium-anreichernden Läsionen, unter Placebo waren es 72 %. Das Ausbleiben neuer hyperintenser T2-Läsionen wurde bei 57 % der Patienten unter Natalizumab und bei 15 % unter Placebo beobachtet.
- Post-hoc-Subgruppenanalysen ergaben in der kleinen Gruppe von Patienten mit weniger als neun hyperintensiven T2-Läsionen keine Veränderung der Progression der Behinderung.

- In der Subgruppe von Patienten mit hochaktiver schubförmig remittierender MS, definiert durch mindestens zwei Schübe im vorangegangenen Jahr und mindestens eine Gadoliniumgegenüber 1,5 (n=61) unter Placebo. Die relative Risikoreduktion für eine Behinderungsprogression betrug 64 %.
- Die EMEA bewertet das Vorgehen einer nachträglichen Subgruppenanalyse durchaus kritisch. Der Therapieeffekt in der Subgruppe der Patienten mit hochaktiver schubförmig remittierender MS wurde jedoch als so hoch eingeschätzt, dass für diese Patientengruppe eine Zulassung auch ohne Vortherapie mit Immunmodulatoren erging.
- Bei der SENTINEL-Studie (Rudick et al.) handelte es sich um eine Kombinationstherapie-Studie, in der Patienten, die trotz einer Behandlung mit Interferon Beta mindestens einen Schub im vorangegangenen Jahr erlitten hatten, zusätzlich Natalizumab erhielten. Hierunter traten zwei Fälle einer PML auf, sodass aus Sicherheitsgründen eine Zulassung für diese Kombination nicht erfolgte. Die Studie hatte die gleichen Endpunkte wie die AFFIRM Studie.
- Das Risiko einer Behinderungsprogression wurde nach zwei Jahren ebenfalls signifikant – jedoch weniger stark – um 6 % gesenkt. Während es unter Monotherapie mit Interferon Beta bei 29 % der Patienten zu einer Progression kam, waren es unter Natalizumab in Kombination mit Interferon Beta nur 23 %. Dies entspricht einer NNT von 17 und einer relativen Risiko-reduktion von 24 %.
- Nach Einschätzung der EMEA ist der Anteil, den Natalizumab an diesem Ergebnis hat, nicht bestimmbar, da ein Natalizumab-Monotherapiearm in der Studie fehlte. Dennoch war dieses Studienergebnis Grundlage der Zulassung als Monotherapie für Patienten mit nur einem Schub im vorangegangenen Jahr unter Interferontherapie.
- *Empfehlungen zur wirtschaftlichen Verordnungsweise*
- Es sollten deshalb nur solche Patienten mit Natalizumab behandelt werden, bei denen Kontraindikationen oder Unverträglichkeiten für Interferon (IFN) beta oder/und Glatirameracetat bestehen oder die im Verlauf eines Jahres auf Interferon Beta oder/und Glatirameracetat nicht ausreichend angesprochen haben und die für eine Eskalationstherapie mit Mitoxantron unter Berücksichtigung seiner Zulassung und Risiken nicht geeignet sind.

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## G-BA, 2012 [6].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 2. August 2012 - Fampridin

### Anwendungsgebiet

Fampyra® ist zur Verbesserung der Gehfähigkeit von erwachsenen Patienten mit Multipler Sklerose (MS) mit Gehbehinderung indiziert (EDSS 4-7)

### Zweckmäßige Vergleichstherapie

Die zweckmäßige Vergleichstherapie zur Verbesserung der Gehfähigkeit von erwachsenen Patienten mit Multipler Sklerose (MS) ist Krankengymnastik entsprechend der Heilmittelrichtlinie unter der Voraussetzung einer optimierten MS-Standardtherapie (einschließlich einer symptomatischen Therapie mit gegebenenfalls Spasmolytika).

### Fazit / Ausmaß des Zusatznutzens

Da die erforderlichen Nachweise nicht vollständig vorgelegt worden sind, gilt der Zusatznutzen im Verhältnis zur zweckmäßigen Vergleichstherapie als nicht belegt

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#### G-BA, 2014 [11].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 20. März 2014 - Teriflunomid

#### Anwendungsgebiet

**Teriflunomid** (Aubagio®) ist angezeigt zur Behandlung erwachsener Patienten mit schubförmig-remittierender Multipler Sklerose (MS).

#### Vergleichstherapie

Die zweckmäßige Vergleichstherapie für die Behandlung von erwachsenen Patienten mit schubförmig-remittierender Multipler Sklerose (MS) ist Beta-Interferon (IFN-β) 1a oder IFN-β 1b oder Glatirameracetat unter Beachtung des jeweils zugelassenen Anwendungsgebietes.

### Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen ist nicht belegt.

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#### G-BA, 2016 [8].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 16. Oktober 2014 / 8. Januar 2015 / 23. Juni 2015 / 7. Januar 2016 - Dimethylfumarat

#### Anwendungsgebiet

Dimethylfumarat (Tecfidera®) wird zur Behandlung von erwachsenen Patienten mit schubförmig remittierender Multipler Sklerose angewendet.

#### Vergleichstherapie

Die zweckmäßige Vergleichstherapie für Dimethylfumarat zur Behandlung von Patienten mit schubförmig remittierender Multiplen Sklerose (RRMS) ist:

- Interferon beta-1a oder Interferon beta-1b oder Glatirameracetat.

### Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen gegenüber Beta-Interferon 1a ist nicht belegt.

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#### G-BA, 2016 [5].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 1. Oktober 2015 / 19. Mai 2016 - Fingolimod

### Anwendungsgebiet

Gilenya ist als krankheitsmodifizierende Monotherapie von hochaktiver schubförmig-remittierend verlaufender Multipler Sklerose bei folgenden Gruppen erwachsener Patienten angezeigt:

- Patienten mit hochaktiver Erkrankung trotz Behandlung mit einem vollständigen und angemessenen Zyklus mit mindestens einer krankheitsmodifizierenden Therapie

Oder

- Patienten mit rasch fortschreitender schwer schubförmig-remittierend verlaufender Multipler Sklerose, definiert durch zwei oder mehr Schübe mit Behinderungsprogression in einem Jahr, und mit einer oder mehr Gadolinium anreichernden Läsionen im MRT des Gehirns oder mit einer signifikanten Erhöhung der T2-Läsionen im Vergleich zu einer kürzlich durchgeföhrten MRT.

### Vergleichstherapie

- Glatirameracetat oder Interferon-beta (IFN-β) 1a oder 1b, Umstellung in Abhängigkeit von der Vortherapie, ggf. Fortführung bzw. Anpassung der vorangegangenen Therapie
- Patientenindividuelle Therapie unter Berücksichtigung der Vortherapie und der Zulassung.

### Fazit / Ausmaß des Zusatznutzens / Ergebnis

- Ein Zusatznutzen ist nicht belegt.
- Ein Zusatznutzen ist nicht belegt.

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### G-BA, 2016 [3].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage IV – Therapiehinweis Alemtuzumab vom 15. September 2016

### Fazit

Am 12. September 2013 wurde Alemtuzumab mit dem Handelsnamen Lemtrada® zugelassen zur Behandlung von Erwachsenen mit schubförmig-remittierender Multipler Sklerose (RRMS) mit aktiver Erkrankung, definiert durch klinischen Befund oder Bildgebung.

Die Anwendung von Alemtuzumab wird nicht empfohlen bei Patientinnen und Patienten, die keine aktive Erkrankung aufweisen oder unter der aktuellen Therapie stabil sind.

### Empfehlungen zur wirtschaftlichen Verordnungsweise (*Auszug*)

Vor der Behandlung müssen die Patientinnen und Patienten über

- die Risiken und den Nutzen der Behandlung sowie
- die Notwendigkeit einer 48-monatigen Nachbeobachtung nach der letzten Alemtuzumab-Infusion aufgeklärt werden.

Mit Alemtuzumab behandelten Patientinnen und Patienten müssen

- die Packungsbeilage,
- die Patientenkarte und
- der Leitfaden für Patientinnen und Patienten ausgehändigt werden.

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## G-BA, 2019 [10].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 20. Juni 2019 - Fingolimod (neues Anwendungsgebiet: pädiatrische Patienten mit hochaktiver schubförmig-remittierender Multipler Sklerose)

### Anwendungsgebiet

Gilenya ist als krankheitsmodifizierende Monotherapie von hochaktiver schubförmig remittierend verlaufender Multipler Sklerose bei folgenden Gruppen erwachsener Patienten und Kindern und Jugendlichen ab einem Alter von 10 Jahren angezeigt:

A1) Patienten mit hochaktiver Erkrankung trotz Behandlung mit einem vollständigen und

angemessenen Zyklus mit mindestens einer krankheitsmodifizierenden Therapie

oder

A2) Patienten mit rasch fortschreitender schwerer schubförmig-remittierend verlaufender Multipler Sklerose, definiert durch zwei oder mehr Schübe mit Behinderungsprogression in einem Jahr, und mit einer oder mehr Gadolinium anreichernden Läsionen im MRT des Gehirns oder mit einer signifikanten Erhöhung der T2-Läsionen im Vergleich zu einer kürzlich durchgeführten MRT.

### Zweckmäßige Vergleichstherapie

A1) Kinder und Jugendliche von  $\geq 10$  und  $< 18$  Jahren mit hochaktiver schubförmig remittierend verlaufender Multipler Sklerose trotz Behandlung mit einem vollständigen und angemessenen Zyklus mit mindestens einer krankheitsmodifizierenden Therapie, für die eine Eskalation der Therapie angezeigt ist.

- Therapie nach Maßgabe des Arztes

A2) Kinder und Jugendliche von  $\geq 10$  und  $< 18$  Jahren mit hochaktiver schubförmig remittierend verlaufender Multipler Sklerose trotz Behandlung mit einem vollständigen und angemessenen Zyklus mit mindestens einer krankheitsmodifizierenden Therapie, für die ein Wechsel innerhalb der Basistherapeutika angezeigt ist.

- Interferon beta-1a oder Interferon beta-1b oder Glatirameracetat, unter Berücksichtigung des Zulassungsstatus

B1) Kinder und Jugendliche von  $\geq 10$  und  $< 18$  Jahren mit rasch fortschreitender schwerer schubförmig-remittierend verlaufender Multipler Sklerose, definiert durch zwei oder mehr Schübe mit Behinderungsprogression in einem Jahr, und mit einer oder mehr Gadolinium-anreichernden Läsionen im MRT des Gehirns oder mit einer signifikanten Erhöhung der T2-Läsionen im Vergleich zu einer kürzlich durchgeführten MRT, die bislang noch keine krankheitsmodifizierende Therapie erhalten haben.

- Interferon beta-1a oder Interferon beta-1b oder Glatirameracetat, unter Berücksichtigung des Zulassungsstatus

Kinder und Jugendliche von  $\geq 10$  und  $< 18$  Jahren mit rasch fortschreitender schwerer schubförmig-remittierend verlaufender Multipler Sklerose, definiert durch zwei oder mehr Schübe mit Behinderungsprogression in einem Jahr, und mit einer oder mehr Gadolinium-anreichernden Läsionen im MRT des Gehirns oder mit einer signifikanten Erhöhung der T2-Läsionen im Vergleich zu einer kürzlich durchgeführten MRT trotz krankheitsmodifizierender Therapie.

- Therapie nach Maßgabe des Arztes

#### Fazit / Ausmaß des Zusatznutzens

- A1) Ein Zusatznutzen ist nicht belegt.
- A2) Anhaltspunkt für einen nicht quantifizierbaren Zusatznutzen
- B1) Anhaltspunkt für einen nicht quantifizierbaren Zusatznutzen.
- B2) Ein Zusatznutzen ist nicht belegt.

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#### G-BA, 2018 [9].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 17. Mai 2018 / 21. Juni 2018 - Cladribin

#### Anwendungsgebiet

MAVENCLAD wird angewendet zur Behandlung von erwachsenen Patienten mit hochaktiver schubförmiger Multipler Sklerose (MS), definiert durch klinische oder bildgebende Befunde

#### Vergleichstherapie

Die zweckmäßige Vergleichstherapie für Cladribin zur Behandlung von erwachsenen Patienten mit hochaktiver schubförmiger Multipler Sklerose, definiert durch klinische oder bildgebende Befunde, ist:

- a) für Patienten, die bislang noch keine krankheitsmodifizierende Therapie erhalten haben
  - Interferon beta-1a oder Interferon beta-1b oder Glatirameracetat unter Berücksichtigung der Zulassung
- b) für Patienten mit hochaktiver Erkrankung trotz Behandlung mit einer krankheits-modifizierenden Therapie
  - Alemtuzumab oder Fingolimod oder Natalizumab oder, sofern angezeigt, Wechsel innerhalb der Basistherapeutika (Interferon beta-1a oder Interferon beta-1b oder Glatirameracetat unter Berücksichtigung der Zulassung)

#### Fazit / Ausmaß des Zusatznutzens / Ergebnis

- a) Ein Zusatznutzen ist nicht belegt.
- b) Ein Zusatznutzen ist nicht belegt.

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#### G-BA, 2018 [7].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 2. August 2018 - Ocrelizumab

#### Anwendungsgebiet

Ocrevus® ist angezeigt zur Behandlung erwachsener Patienten mit schubförmiger Multipler Sklerose (RMS) mit aktiver Erkrankung, definiert durch klinischen Befund oder Bildgebung

Ocrevus® ist angezeigt zur Behandlung erwachsener Patienten mit früher primär progredienter Multipler Sklerose (PPMS), charakterisiert anhand der Krankheitsdauer und

dem Grad der Behinderung, sowie mit Bildgebungsmerkmalen, die typisch für eine Entzündungsaktivität sind

### Vergleichstherapie

- a) Erwachsene Patienten mit schubförmiger Multipler Sklerose (RMS) mit aktiver Erkrankung, die bislang noch keine krankheitsmodifizierende Therapie erhalten haben oder mit krankheitsmodifizierender Therapie vorbehandelte erwachsene Patienten, deren Erkrankung nicht hochaktiv ist
  - o Interferon beta-1a oder Interferon beta-1b oder Glatirameracetat unter Berücksichtigung der Zulassung
- b) Erwachsene Patienten mit schubförmiger Multipler Sklerose (RMS) mit hochaktiver Erkrankung trotz Behandlung mit einer krankheitsmodifizierenden Therapie
  - o Alemtuzumab oder Fingolimod oder Natalizumab oder, sofern angezeigt, Wechsel innerhalb der Basistherapeutika (Interferon beta-1a oder Interferon beta-1b oder Glatirameracetat unter Berücksichtigung der Zulassung)
- c) Erwachsene Patienten mit früher primär progredienter Multipler Sklerose (PPMS), charakterisiert anhand der Krankheitsdauer und dem Grad der Behinderung, sowie mit Bildgebungsmerkmalen, die typisch für eine Entzündungsaktivität sind:
  - o Best-Supportive-Care

### Fazit / Ausmaß des Zusatznutzens / Ergebnis

- a) Beleg für einen geringen Zusatznutzen.
- b) Ein Zusatznutzen ist nicht belegt.
- c) Anhaltspunkt für einen geringen Zusatznutzen.

## 3.2 Cochrane Reviews

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**La Mantia L et al., 2016 [14].**

Interferons-beta versus glatiramer acetate for relapsing-remitting multiple sclerosis (Review)

*Update vom Cochrane Review 'Interferons-beta versus glatiramer acetate for relapsing-remitting multiple sclerosis' (first published in the Cochrane Library 2014, Issue 7)*

### Fragestellung

To assess whether IFNs-beta and GA differ in terms of efficacy and safety in the treatment of people with relapsing-remitting (RR) MS.

### Methodik

#### Population:

- Patienten mit RRMS

#### Intervention:

- IFNs-beta (IFN-beta 1a (Rebif®, Avonex®) or IFN-beta 1b (Betaferon®, Betaseron ®, Extavia®))

#### Komparator:

- GA

#### Endpunkte:

- Primäre Endpkt.: Number of participants who experienced at least one relapse at 12 to 24 months and at the end of follow-up; number of participants whose condition worsened during the study; Number of participants who withdrew from or dropped out of the study because of adverse events (AEs)
- Sekundäre Endpkt.: u.a. Frequency of relapse, Time to first relapse after the start of the study, Percentage of participants free of disease activity

#### Recherche/Suchzeitraum:

- Systematische Recherche bis 8. August 2016

#### Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool

### Ergebnisse

#### Anzahl eingeschlossener Studien:

- 6 RCTs (n=2904)

#### Charakteristika der Population:

- 2 Studien: compared the effects of GA versus IFN-beta 1b (Cadavid 2009a; O'Connor 2009a)
- 4 Studien: compared GA versus IFN-beta 1a (Calabrese 2012; Lublin 2013a; Mikol 2008; NCT01058005), with two comparing GA versus IFN-beta 1a 44 mcg SC (Mikol 2008;

NCT01058005), one GA versus IFN-beta 1a 30 mcg IM (Lublin 2013a), one GA versus both IFN-beta 1a 44 mcg SC and IFN-beta 1a 30mcg IM(Calabrese 2012), and one comparing GA versus IFN-beta 1a 44mcg SCand natalizumab (NCT01058005)

- The RCTs included in the review were homogeneous in terms of included populations, treatment schedules and outcome measures. All studies included only participants with active RRMS (prestudy relapse frequency ranging from 0.97 to 1.9) and low disability (EDSS 1.9 to 2.35).
- A total of 2904 participants were randomly assigned to IFNs (n=1704) and GA (n=1200).

#### Qualität der Studien:

- The risk of bias was variable across studies: incomplete outcome data was the main biased dimension (high risk of bias in all studies) because of high levels of dropout and missing data, followed by lack of blinding of participants and investigators and by selective outcome reporting (high risk of bias in three and two studies, respectively).
- All studies were at high risk for attrition bias.
- The quality of evidence for primary outcomes was judged as moderate for clinical end points, but for safety and some MRI outcomes (number of active T2 lesions), quality was judged as low.

#### Studienergebnisse:

##### **Number of participants who experienced at least one relapse at 12 months or at 24 months or at the end of follow-up**

- no significant differences in effect at 24 months (RR 1.04, 95% CI 0.87 to 1.24; 3 Studien [2184 Patienten]) and at 36 months (RR 1.27, 95% CI 0.92 to 1.75; 1 Studie [509 Patienten]).

##### **Number of participants with confirmed worsening at 12 months or at 24 months or at the end of follow-up**

- no significant differences were found when confirmed progression was analysed at 24 months (RR 1.11, 95% CI 0.91 to 1.35; 3 Studien [2169 Patienten]) or at 36 months (RR 0.87, 95% CI 0.63 to 1.20; 1 Studie [487 Patienten])

##### **Number of participants who withdrew from or dropped out of the study because of adverse events**

- no significant differences were found between the two treatment groups (RR 0.95, 95% CI 0.64 to 1.40; 4 Studien [2685 Patienten]).
- Similar results were found when SAEs were considered (RR 0.99, 95% CI 0.63 to 1.56; 4 Studien [2685 Patienten]).

#### **Frequency of relapse**

- The rate ratio (1.06, 95% CI 0.95 to 1.18; 4 Studien) showed no difference between the two groups.
- At 36 months, data were provided by one study (Lublin 2013a); the rate ratio (1.40, 95% CI 1.13 to 1.74) was significantly higher in the IFN group (P value 0.002), favouring GA

#### **Time to first relapse**

- No differences were found (HR 1.01, 95% CI 0.87 to 1.16) without heterogeneity among studies

### Secondary magnetic resonance imaging (MRI) outcomes

- Secondary magnetic resonance imaging (MRI) outcomes analysis showed that effects on new or enlarging T2- or new contrast-enhancing T1 lesions at 24 months were similar (mean difference (MD) -0.15, 95% CI -0.68 to 0.39, and MD -0.14, 95% CI -0.30 to 0.02, respectively). However, the reduction in T2- and T1-weighted lesion volume was significantly greater in the groups given IFNs than in the GA groups (MD -0.58, 95% CI -0.99 to -0.18, P value 0.004, and MD -0.20, 95% CI -0.33 to -0.07, P value 0.003, respectively).

### Anmerkung/Fazit der Autoren

The effects of IFNs-beta and GA in the treatment of people with RRMS, including clinical (e.g. people with relapse, risk to progression) and MRI (Gd-enhancing lesions) measures, seem to be similar or to show only small differences. When MRI lesion load accrual is considered, the effect of the two treatments differs, in that IFNs-beta were found to limit the increase in lesion burden as compared with GA. Evidence was insufficient for a comparison of the effects of the two treatments on patient-reported outcomes, such as quality of life measures.

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### La Mantia L et al., 2016 [15].

Fingolimod for relapsing-remitting multiple sclerosis (Review)

### Fragestellung

To assess the safety and benefit of fingolimod versus placebo, or other disease-modifying drugs (DMDs), in reducing disease activity in people with relapsing-remitting multiple sclerosis (RRMS).

### Methodik

#### Population:

- Patienten mit RRMS

#### Intervention:

- Fingolimod

#### Komparator:

- Placebo oder DMDs

#### Endpunkte:

- Primäre Endpkt.: Number of participants relapse-free at six, 12 and 24 months after randomisation and at the end of follow-up; Number of participants free from disability worsening at 12, 24 and 36 months after randomisation and at the end of follow-up; Number of participants who withdrew from the study due to adverse events and serious adverse events
- Sekundäre Endpkt.: u.a. Annualised relapse rate at six, 12 and 24 months after randomisation and at the end of follow-up; Number of participants free from MRI gadolinium-enhancing lesions at six, 12 and 24 months after randomisation and at the end of follow-up.

Recherche/Suchzeitraum:

- Systematische Recherche bis 15 Februar 2016

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool

**Ergebnisse**

Anzahl eingeschlossener Studien:

- 6 RCTs (n=5152)

Charakteristika der Population:

- 4 Studien: compared fingolimod to placebo (Calabresi 2014; Kappos 2006; Kappos 2010; Saida 2012),
- 1 Studie: compared fingolimod to intramuscular interferon beta-1a (Cohen 2010),
- 1 Studie compared fingolimod to other DMDs (interferon beta-1a, interferon beta-1b, glatiramer acetate)

Qualität der Studien:

- We downgraded the quality of the evidence for all included outcomes at 24 months due to significant differences in reasons of incomplete outcome data between fingolimod 0.5mg and placebo groups. We further downgraded the quality of evidence for disability worsening, withdrawals due to adverse events, and MRI gadolinium-enhancing lesions due to insufficient information size and wide confidence intervals. We further downgraded the quality of evidence for withdrawals due to inconsistency.
- Overall we gave a GRADE rating of moderate for relapses, low for disability progression, very low for withdrawals due to adverse events, and low for MRI gadolinium-enhancing lesions .

Studienergebnisse zum Vergleich Fingolimod vs intramuscular interferon beta-1a or other DMDs:

**Number of participants relapse-free at six,12 and 24 months after randomisation and at the end of follow-up**

- Data from one trial were available to evaluate the primary outcomes during the first 1 2months of treatment with fingolimod 0.5 mg compared to intramuscular interferon beta-1a (Cohen 2010).
- The overall results (RR 1.18, 95% CI 1.09 to 1.27; moderate quality evidence) indicated a slight advantage for fingolimod 0.5 mg in favouring freedom from relapse
- Similar results were found when fingolimod was used at 1.25 mg (RR 1.15, 95% CI 1.06 to 1.24)

**Number of participants free from disability worsening at 12, 24 and 36 months after randomisation and at the end of follow-up**

- The results indicated no difference in favouring freedom from disability worsening at 12months between fingolimod 0.5mg and intramuscular interferon beta-1a (RR 1.02, 95% CI 0.99 to 1.06; low quality evidence)

- Similar results were found when fingolimod was used at 1.25 mg (RR 1.01, 95% CI 0.98 to 1.05)

**Number of participants who withdrew from the study due to adverse events and serious adverse events**

- Compared to intramuscular interferon beta-1a, the number of participants who withdrew due to adverse events was higher, but not significant for fingolimod 0.5 mg (RR 1.51, 95% CI 0.81 to 2.80; moderate quality evidence)
- Significant risk was found when used at 1.25 mg (RR 2.69, 95% CI 1.54 to 4.72)
- Compared to intramuscular interferon beta-1a, the number of participants who withdrew due to serious adverse events was higher, but not significant for fingolimod 0.5 mg (RR 1.21, 95% CI 0.72 to 2.02), and significantly higher for fingolimod 1.25 mg (RR 1.85, 95% CI 1.15 to 2.96)

**Annualised relapse rate at six, 12 and 24 months after randomisation and at the end of follow-up**

- The annualised relapse rate was evaluated by one trial at 12 months (Cohen 2010). A significant benefit for fingolimod 0.5 mg (RR 0.48, 95% CI 0.34 to 0.70) and fingolimod 1.25 mg (RR 0.61, 95% CI 0.47 to 0.78) doses compared to intramuscular interferon beta-1a was observed

**Number of participants free from MRI gadolinium-enhancing lesions at six, 12 and 24 months after randomisation and at the end of follow-up.**

- The number of participants free from MRI gadolinium-enhancing lesions at 12 months was evaluated by the same trial (Cohen 2010); a slight advantage for fingolimod 0.5 mg (RR 1.12, 95% CI 1.05 to 1.19) and fingolimod 1.25 mg (RR 1.13, 95% CI 1.06 to 1.20) compared to intramuscular interferon beta-1a was observed

**Anmerkung/Fazit der Autoren**

The direct comparison with other approved first-line DMDs, in particular intramuscular interferon beta-1a, indicates a higher benefit of fingolimod in terms of relapse prevention, but a significant risk of discontinuation in the first months of treatment. A higher incidence of adverse events was found, suggesting lower tolerability for fingolimod versus interferon beta-1a, requiring careful monitoring over time.

However, the data were inadequate, for the low number of head-to-head RCTs and types of comparisons, with short follow-up duration.

*Kommentare zum Review*

- Berichtet wurden ausschließlich die Ergebnisse der direkt vergleichenden Studien

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**He D et al., 2016 [12].**

Teriflunomide for multiple sclerosis

**Fragestellung**

To assess the absolute and comparative effectiveness and safety of teriflunomide as monotherapy or combination therapy versus placebo or other disease-modifying drugs

(DMDs) (interferon beta (IFN), glatiramer acetate, natalizumab, mitoxantrone, fingolimod, dimethyl fumarate, alemtuzumab) for modifying the disease course in people with MS.

## Methodik

### Population:

- Patienten mit MS

### Intervention:

- Teriflunomid als Mono- oder Kombinationstherapie

### Komparator:

- Placebo oder DMDs

### Endpunkte:

- Primäre Endpkt.: The proportion of participants with at least one relapse at one year or two years; The proportion of participants with disability progression as assessed by the EDSS; The number of participants with adverse events (AEs), number of participants with serious adverse events (SAEs), and number of participants who withdrew or dropped out from the study because of AEs at one year or two years.
- Sekundäre Endpkt.: u.a. The annualized relapse rate at one year or two years; The number of gadolinium-enhancing T1-weighted lesions at one year or two years; Mean change in HRQoL

### Recherche/Suchzeitraum:

- Systematische Recherche bis 30. September 2015

### Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool

## Ergebnisse

### Anzahl eingeschlossener Studien:

- 5 RCTs (n=3231)

### Charakteristika der Population:

- 2 Studien: compared teriflunomide 7mg/day or 14 mg/day versus placebo for 2257 adults with relapsing forms of MS (Confavreux 2014; O'Connor 2011)
- 2 Studien: compared teriflunomide 7mg/day or 14 mg/day with add-on IFN versus placebo in 650 people with relapsing MS (Freedman 2012; NCT01252355)
- 1 Studie: teriflunomide 7 mg/day or 14 mg/ day in comparison to IFN -1a in 324 people with relapsing MS (Vermersch 2014)

### Qualität der Studien:

- All studies had a high risk of detection bias for relapse assessment and a high risk of bias due to conflicts of interest. Among them, three studies also had a high risk of attrition bias due to a high dropout rate and two studies had an unclear risk of attrition bias. Generally, the higher the ratio of participants with missing data to participants with events, the greater

potential there is for bias, especially for the high frequency of events. The potential impact of missing continuous outcomes increases with the proportion of participants with missing data. In addition, the studies of combination therapy with IFN and the study with IFN-1a as controls also had a high risk of performance bias and a lack of power due to the limited sample. The evidence in this review was mainly derived from the two large-scale RCTs, in which the high risk of bias lead to low quality evidence for the results of relapse. The results of disability progression were also subjected to a serious indirectness of evidence because disability progression was confirmed in less than six months in both studies. The evidence for disability progression was very low.

**Studienergebnisse:**

**proportion of participants with at least one relapse at one year or two years**

- When administrated as monotherapy for 48 weeks to 115 weeks in Vermersch 2014, low dose of teriflunomide was inferior to IFN-1a on the proportion of participants with at least one relapse (RR 2.74, 95% CI 1.66 to 4.53, P value < 0.0001; 213 participants), but there was no difference in reducing the number of participants with at least one relapse for high dose of teriflunomide (RR 1.52, 95% CI 0.87 to 2.67, P value = 0.14; 215 participants).

**The number of participants with adverse events (AEs), number of participants with serious adverse events (SAEs), and number of participants who withdrew or dropped out from the study because of AEs at one year or two years.**

- Vermersch 2014 reported the safety of teriflunomide as monotherapy after the core treatment period of 48 weeks to 115 weeks. Compared to IFN-1a, there was no difference for both doses of teriflunomide in the incidence of AEs (low dose: RR 0.97, 95% CI 0.92 to 1.04, P value = 0.43; 211 participants; high dose: RR 0.97, 95% CI 0.90 to 1.03, P value = 0.29; 211 participants) or SAEs (low dose: RR 1.57, 95% CI 0.64 to 3.84, P value = 0.32; high dose: RR 0.79, 95% CI 0.27 to 2.26, P value = 0.66).
- However, the incidence of AEs leading to discontinuation in the IFN group was higher than those in the teriflunomide groups (low dose: RR 0.38, 95% CI 0.18 to 0.78, P value = 0.008; high dose: RR 0.50, 95% CI 0.26 to 0.96, P value = 0.04).
- The most commonly reported AEs (10% or greater) in either teriflunomide group were nasopharyngitis, headache, paraesthesia, diarrhoea, hair thinning, back pain and elevated ALT levels. Among these AEs, the incidence of diarrhoea in both teriflunomide groups was higher than that in the IFN-1a group (low dose: RR 2.87, 95% CI 1.36 to 6.07, P value = 0.006; high dose: RR 2.64, 95% CI 1.24 to 5.63, P value = 0.01). Compared to IFN-1a, hair thinning was more common with high-dose teriflunomide rather than low-dose teriflunomide (RR 20.20, 95% CI 2.77 to 147.14, P value = 0.003).
- However, elevated ALT levels occurred with a lower frequency in the teriflunomide groups (low dose: RR 0.36, 95% CI 0.19 to 0.65, P value = 0.0009; high dose: RR 0.33, 95% CI 0.17 to 0.61, P value = 0.0005). In addition, influenza-like illness was reported more frequently with IFN-1a than with teriflunomide (low dose: RR 0.07, 95% CI 0.03 to 0.18, P value < 0.00001; high dose: RR 0.05, 95% CI 0.02 to 0.16, P value < 0.00001). There was a similar incidence of other AEs between the IFN-1a group and teriflunomide groups.

**Annualized relapse rate**

- Vermersch 2014 reported the data of annualized relapse rate after the treatment period of 48 weeks to 115 weeks (low dose: annualized relapse rate 0.41, 95% CI 0.27 to 0.64; 109 participants; high dose: annualized relapse rate 0.26, 95% CI 0.15 to 0.44; 111 participants;

IFN-1a: annualized relapse rate 0.22, 95% CI 0.11 to 0.42; 104 participants). However, we could not calculate the total number of relapses and the standard error due to the variable duration of follow-up, consequently we could not calculate the rate ratio. However, the authors reported the RR on annualized relapse rate, showing that low-dose teriflunomide was inferior to IFN-1a on annualized relapse rate (RR 1.90, 95% CI 1.05 to 3.43, P value = 0.03; 213 participants), but there was no difference in reducing annualized relapse rate for high-dose teriflunomide (RR 1.20, 95%CI 0.62 to 2.30, P value = 0.59; 215 participants).

### Anmerkung/Fazit der Autoren

There was low-quality evidence to support that teriflunomide at a dose of 7 mg/day or 14 mg/day as monotherapy reduces both the number of participants with at least one relapse and the annualized relapse rate over one year or two years of treatment in comparison with placebo. Only teriflunomide at a dose of 14 mg/day reduced the number of participants with disability progression and delayed the progression of disability over one year or two years, but the quality of the evidence was very low. The quality of available data was too low to evaluate the benefit teriflunomide as monotherapy versus IFN-1a or as combination therapy with IFN. The common adverse effects were diarrhoea, nausea, hair thinning, elevated alanine aminotransferase, neutropenia and lymphopenia. These adverse effects were mostly mild-to-moderate in severity, but had a dose-related effect. New studies of high quality and longer follow-up are needed to evaluate the comparative benefit of teriflunomide on these outcomes and the safety in comparison with other DMTs.

### Kommentare zum Review

- Autoren haben eine Metaanalyse gemacht, da: high risk of bias and clinical diversities of the included studies
- Berichtet wird nur die vergleichende Studie von (Vermersch 2014): teriflunomide 7 mg/day or 14 mg/ day in comparison to IFN -1a in 324 people with relapsing MS
- In der Studie finden sich keine Angaben zur Lebensqualität

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### Riera R et al., 2016 [23].

Alemtuzumab for multiple sclerosis.

Siehe auch: Zhang J et al., 2017 [30].

### Fragestellung

To assess the safety and effectiveness of alemtuzumab used alone or associated with other treatments to decrease disease activity in patients with any form of MS.

### Methodik

#### Population:

- Patienten mit MS

#### Intervention:

- Alemtuzumab als Mono- oder Kombinationstherapie

Komparator:

- Placebo, any other active drug therapy (i.e. corticosteroids, plasmapheresis, beta interferons, glatiramer acetate, fingolimod, natalizumab, mitoxantrone, teriflunomide or dimethyl fumarate).

Endpunkte:

- Primäre Endpkt.: Relapse-free survival; Sustained disease progression-free survival; Number of participants with at least one adverse event, including serious adverse events
- Number of participants relapse-free at six, 12 and 24 months after randomisation and at the end of follow-up; Number of participants free from disability worsening at 12, 24 and 36 months after randomisation and at the end of follow-up; Number of participants who withdrew from the study due to adverse events and serious adverse events
- Sekundäre Endpkt.: u.a. Number of participants free of clinical disease activity; Quality of life

Recherche/Suchzeitraum:

- Systematische Recherche bis 30. April 2015

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool

**Ergebnisse**

Anzahl eingeschlossener Studien:

- 6 RCTs (n=1713)

Charakteristika der Population:

- Alle Studien vergleichen Alemtuzumab vs subcutaneous interferon beta-1a
- Participants were treatment-naïve in the CARE-MS I and CAMMS223 studies. The CARE-MS II study included only participants with at least one relapse while being treated with interferon beta or glatiramer for at least six months.

Qualität der Studien:

- The overall quality of the studies was low since in all of them we categorised at least one of the main domains (generation of allocation sequence, allocation concealment and blinding) as having a high risk of bias.

Studienergebnisse

**Relapse-free survival**

- Alemtuzumab was associated with better relapse-free survival at 24-month follow-up (hazard ratio (HR) 0.50, 95% confidence interval (CI) 0.41 to 0.60; 1248 participants; two studies; moderate quality evidence, I<sup>2</sup> = 0%)
- Only one study assessed this outcome at 36 months (CAMMS223). This study showed a higher number of participants who relapsed with interferon than with alemtuzumab (45 versus 24; HR 0.31, 95% CI 0.18 to 0.52).

**Sustained disease progression-free survival**

- Alemtuzumab was associated with a lower number of participants with sustained disease progression-free survival at both 24-month (HR 0.62, 95% CI 0.44 to 0.87; 1191 participants; two studies; I<sup>2</sup> = 0%) and 36-month follow-up (HR 0.25, 95% CI 0.11 to 0.57; 223 participants; one study)
- For naive participants there was no difference between the interventions.

**Number of participants with at least one adverse event, including serious adverse events**

- Alemtuzumab was associated with a higher proportion of participants with at least one adverse event after 24 months (risk ratio (RR) 1.04, 95% CI 1.01 to 1.06; 1248 participants; two studies; I<sup>2</sup> = 0%; moderate quality evidence), but not at 36 months (RR 1.00, 95% CI 0.98 to 1.02; 224 participants; one study)

**Number of participants free of clinical disease activity**

- None of the included studies assessed this outcome.

**Quality of life**

- None of the included studies assessed this outcome.

**Change in disability as assessed by the Expanded Disability Status Scale (EDSS)**

- Alemtuzumab was associated with a significant improvement in EDSS scores after 36 months (mean difference (MD) -0.70, 95% CI -1.04 to -0.36; 223 participants; one study) (CAMMS223).
- At 24months, considering both treatment-naive patients and previously treated patients (who failed after interferon beta or glatiramer treatment), there were no differences in EDSS scores (MD -0.20, 95% CI -0.60 to 0.20; 1199 participants; two studies; I<sup>2</sup> = 88%) (Analysis 1.4). However, when only previously treated patients were assessed, alemtuzumab was associated with better results (MD -0.41, 95% CI -0.62 to -0.20; one study; 628 participants) (CARE-MS II).

**Anmerkung/Fazit der Autoren**

In patients with relapsing-remitting MS, alemtuzumab 12 mg was better than subcutaneous interferon beta-1a for the following outcomes assessed at 24 months: relapse-free survival, sustained disease progression-free survival, number of participants with at least one adverse event and number of participants with new or enlarging T2-hyperintense lesions on MRI. The quality of the evidence for these results was low to moderate.

Alemtuzumab 24 mg seemed to be better than subcutaneous interferon beta-1a for relapse-free survival and sustained disease progression-free survival, at 36 months.

More randomised clinical trials are needed to evaluate the effects of alemtuzumab on other forms of MS and compared with other therapeutic options. These new studies should assess additional relevant outcomes such as the rate of participants free of clinical disease activity, quality of life, fatigue and adverse events (individual rates, serious adverse events and long-term adverse events). Moreover, these new studies should evaluate other doses and durations of alemtuzumab course.

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**Tramacere I et al., 2015 [26].**

Immunomodulators and immunosuppressants for relapsing-remitting multiple sclerosis: a network meta-analysis

## Fragestellung

To compare the benefit and acceptability of interferon beta-1b, interferon beta-1a (Avonex, Rebif), glatiramer acetate, natalizumab, mitoxantrone, fingolimod, teriflunomide, dimethyl fumarate, alemtuzumab, pegylated interferon beta-1a, daclizumab, laquinimod, azathioprine and immunoglobulins for the treatment of people with RRMS and to provide a ranking of these treatments according to their benefit and acceptability, defined as the proportion of participants who withdrew due to any adverse event.

## Methodik

### Population:

- Patienten mit RRMS

### Intervention:

- immunomodulators or immunosuppressants

### Komparator:

- placebo or to another active agent

### Endpunkte:

- Primäre Endpkt.: proportion of participants who experienced new relapses over 12, 24, or 36 months after randomisation or at the end of the study; proportion of participants who experienced disability worsening over 24 or 36 months after randomisation or at the end of the study; treatment discontinuation due to adverse events
- Sekundäre Endpkt.: serious adverse events (SAEs).

### Recherche/Suchzeitraum:

- Systematische Recherche bis 30. September 2014

### Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool

### Netzwerk-Metaanalyse

- We provided estimates from the network meta-analysis based on the methodology developed from the GRADE Working Group (GRADE Working Group 2004, Salanti 2014).

## Ergebnisse

### Anzahl eingeschlossener Studien:

- 39 RCTs (n=25.113)

### Charakteristika der Population:

- Twenty-four (60%) were placebo-controlled and 15 (40%) were head-to-head studies.

### Qualität der Studien:

- we judged three out of 39 (8%) trials at low risk of bias, we judged 16 (41%) at moderate risk of bias, and we judged 20 (51%) at high risk of bias

### Studienergebnisse:

#### **Relapses over 12 months**

- Relapses over 12 months were provided in 29 studies involving 17,897 participants with relapsing-remitting multiple sclerosis (RRMS) (71.3% of the participants in this review)
- Nineteen studies of 12 treatments involving 12,100 participants were placebo-controlled trials, nine studies of 12 treatments involving 4367 participants were head-to-head trials directly comparing active treatments, and one study involving 1430 participants had both a placebo and two active treatment arms. Five of 15 treatments (33%) were compared to placebo only.
- Alemtuzumab was the best drug (risk ratio (RR) versus placebo 0.40, 95% confidence interval (CI) 0.31 to 0.51; SUCRA = 97%; moderate quality evidence), followed by mitoxantrone (RR versus placebo 0.40, 95% CI 0.20 to 0.76; SUCRA = 93%; low quality evidence), natalizumab (RR versus placebo 0.56, 95% CI 0.43 to 0.73; SUCRA = 85%; high quality evidence), and fingolimod (RR versus placebo 0.63, 95% CI 0.53 to 0.74; SUCRA = 80%; low quality evidence). The heterogeneity for this network overall was 0.01, which we considered low heterogeneity.

#### **Relapses over 24 months**

- Relapses over 24 months were provided in 26 studies and 16,800 participants with RRMS (67% of those included in this review)
- Fifteen studies of 12 treatments involving 8562 participants were placebo-controlled trials, nine studies of seven treatments involving 5477 participants were head-to-head trials directly comparing active treatments, and two studies involving 2761 participants had both a placebo and two active treatment arms each. Five of 14 treatments (36%) were compared to placebo only.
- alemtuzumab was the best drug (RR versus placebo 0.46, 95% CI 0.38 to 0.55; SUCRA = 96%; moderate quality evidence), followed by mitoxantrone (RR versus placebo 0.47, 95% CI 0.27 to 0.81; SUCRA = 92%; very low quality evidence), natalizumab (RR versus placebo 0.56, 95% CI 0.47 to 0.66; SUCRA = 88%; high quality evidence), and fingolimod (RR versus placebo 0.72, 95% CI 0.64 to 0.81; SUCRA = 71%; moderate quality evidence). The heterogeneity for this network overall was 0.0036, which we considered low heterogeneity.

#### **Disability worsening over 24 months**

- 24 months was available from 26 studies and 16,800 participants with RRMS (67% of those included in this review)
- Mitoxantrone was the best drug (RR versus placebo 0.20, 95% CI 0.05 to 0.84; SUCRA = 96%; low quality evidence), followed by alemtuzumab (RR versus placebo 0.35, 95% CI 0.26 to 0.48; SUCRA = 94%; low quality evidence), and natalizumab (RR versus placebo 0.64, 95% CI 0.49 to 0.85; SUCRA = 74%; moderate quality evidence). The heterogeneity for this network overall was 0.0081, which we considered low heterogeneity.

#### **Relapses and disability worsening over 36 months**

- Relapses and disability worsening over 36 months were available from two studies only: one on glatiramer acetate versus interferon beta-1a (Avonex), with a RR of 0.71 (95% CI 0.57 to 0.88) for relapses, and a RR of 0.91 (95% CI 0.75 to 1.10) for disability worsening (CombiRx 2013); one on alemtuzumab versus interferon beta-1a (Rebif), with a RR of 0.48

(95% CI 0.33 to 0.68) for relapses, and a RR of 0.42 (95% CI 0.30 to 0.57) for disability worsening (CAMMS223 2008). We judged both studies at high risk of bias

#### Treatment discontinuation due to adverse events over 12 and 24 month

- Acceptability over 12 months was reported in 13 studies on 10 treatments involving 8105 participants: nine studies of seven treatments involving 5718 participants were placebo-controlled trials, and four studies of six treatments involving 2387 participants were head-to-head trials directly comparing active treatments.
- Four of 10 treatments (40%) were compared to placebo only. The majority of direct comparisons between active treatments were not assessed in any trial (Figure 4). The network geometry for acceptability over 24 months was as for relapses and disability worsening over 24 months
- Over 12 months, compared to placebo, several treatments had a significantly higher proportion of participants who withdrew due to any adverse event, such as teriflunomide (RR versus placebo 2.24, 95% CI 1.50 to 3.34), peg-interferon beta (RR versus placebo 2.80, 95% CI 1.39 to 5.64), interferon beta-1a (Avonex) (RR versus placebo 4.36, 95% CI 1.98 to 9.60), interferon beta-1a (Rebif) (RR versus placebo 4.83, 95% CI 2.59 to 9.00), and fingolimod (RR versus placebo 8.26, 95% CI 3.25 to 20.97).
- Over 24 months, the network-meta-analysis showed that, compared to placebo, only fingolimod had a significantly higher proportion of participants who withdrew due to any adverse event (RR versus placebo 1.69, 95% CI 1.32 to 2.17). The heterogeneity for these networks overall was < 0.0001, which we considered low heterogeneity.

#### Serious adverse events (SAEs)

- inconsistency in most comparisons.

#### Anmerkung/Fazit der Autoren

Conservative interpretation of these results is warranted, since most of the included treatments have been evaluated in few trials. The GRADE approach recommends providing implications for practice based on moderate to high quality evidence. Our review shows that alemtuzumab, natalizumab, and fingolimod are the best choices for preventing clinical relapses in people with RRMS, but this evidence is limited to the first 24 months of follow-up. For the prevention of disability worsening in the short term (24 months), only natalizumab shows a beneficial effect on the basis of moderate quality evidence (all of the other estimates were based on low to very low quality evidence).

Currently, therefore, insufficient evidence is available to evaluate treatments for the prevention of irreversible disability worsening. There are two additional major concerns that have to be considered. First, the benefit of all of these treatments beyond two years is uncertain and this is a relevant issue for a disease with a duration of 30 to 40 years. Second, short-term trials provide scanty and poorly reported safety data and do not provide useful evidence in order to obtain a reliable risk profile of treatments. In order to provide longterm information on the safety of the treatments included in this review, it will be necessary also to evaluate non-randomised studies and post-marketing reports released from the regulatory agencies. Finally, more than 70% of the studies included in this review were sponsored by pharmaceutical companies and this may have influenced the results.

There are three needs that the research agenda should address. First, randomised trials of direct comparisons between active agents would be useful, avoiding further placebo-controlled studies. Second, follow-up of the original trial cohorts should be mandatory.

Third, more studies are needed to assess the medium and long-term benefit and safety of immunotherapies and the comparative safety of different agents.

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**Xu Z et al., 2016 [29].**

Dimethyl fumarate for multiple sclerosis

**Fragestellung**

To assess the benefit and safety of dimethyl fumarate as monotherapy or combination therapy versus placebo or other approved disease modifying drugs (interferon beta, glatiramer acetate, natalizumab, mitoxantrone, fingolimod, teriflunomide, alemtuzumab) for patients with MS.

**Methodik**

Population:

- Patienten mit MS

Intervention:

- Dimethyl fumarate als Mono- oder Kombinationstherapie

Komparator:

- Placebo oder DMDs

Endpunkte:

- Primäre Endpkt.: The proportion of patients with at least one relapse at one year or two years; The proportion of patients with disability worsening as assessed by the EDSS at one year or two years; The proportion of patients with at least one adverse event (AE), the proportion of patients with at least one SAE; proportion of patients who discontinued the study drug because of AEs
- Sekundäre Endpkt.: The ARR at one year or two years, defined as the mean number of confirmed relapses per patient; The number (rate) of gadolinium-enhancing T1-weighted lesions at one year or two years; The number (rate) of new or enlarging T2-weighted hyperintense lesions at one year or two years

Recherche/Suchzeitraum:

- Systematische Recherche bis 4. Juni 2014

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool

**Ergebnisse**

Anzahl eingeschlossener Studien:

- 2 RCTs (n=2667)

Charakteristika der Population:

- patients were randomly assigned to high-dose dimethyl fumarate (761), low-dose dimethyl fumarate (773), placebo (773) and glatiramer acetate (360)

- Both studies aimed to evaluate the benefit and safety of dimethyl fumarate as monotherapy

#### Qualität der Studien:

We included two RCTs in this review, involving 2667 adult patients with RRMS to mainly evaluate the benefit and safety of two dosages of dimethyl fumarate (240 mg orally three times daily or twice daily) by direct comparison with placebo. Overall, there were no obvious clinical and methodological heterogeneities between the studies. Both studies had a high attrition bias, resulting in moderate-quality evidence for most primary outcomes. The results of disability worsening were additionally subjected to a serious indirectness of evidence because disability worsening was confirmed in less than six months in both studies. All these factors contributed to a low quality of the evidence for disability worsening. The quality of MRI data reported in the primary studies was poor.

#### Studienergebnisse

##### **The proportion of patients with at least one relapse at two years of follow-up**

- Compared to placebo, the pooled risk ratio (RR) with high-dose dimethyl fumarate administration was 0.57 (95% confidence interval (CI) 0.50 to 0.66,  $P < 0.00001$ ; two studies 1532 participants)
- By contrast, the pooled RR with low dose dimethyl fumarate administration was 0.64 (95% CI 0.54 to 0.77,  $P < 0.00001$ ; two studies 1540 participants)
- Compared to glatiramer acetate, there was a significant difference in reducing the number of patients with relapse for high dosage of dimethyl fumarate ( $RR = 0.75$ , 95% CI 0.59 to 0.96,  $P = 0.02$ ); but no difference for low dosage ( $RR = 0.91$ , 95%CI 0.72 to 1.13,  $P = 0.38$ ). Taking the effect of dropouts into consideration, there was no difference in the likely-case scenario analysis ( $RR = 0.91$ , 95% CI 0.78 to 1.07,  $P = 0.26$  and  $RR = 1.01$ , 95% CI 0.87 to 1.17,  $P = 0.94$ , respectively).

##### **The proportion of patients with disability worsening as assessed by the EDSS at two years of follow-up**

- Disability worsening was confirmed at least 12 weeks (less than six months) in both studies. Based on such data, the risk of disability worsening in participants receiving high-dose and low-dose dimethyl fumarate was 15.77% and 14.58% respectively, which were lower than that in participants receiving placebo (22.31%), the RD was 6.54%and 7.73%respectively.
- Compared to placebo, the pooled RR with high-dose dimethyl fumarate administration was 0.70 (95% CI 0.57 to 0.87,  $P = 0.0009$ ; two studies 1532 participants)
- By contrast, the pooled RR with low dose dimethyl fumarate administration was 0.65 (95% CI 0.53 to 0.81,  $P = 0.0001$ ; two studies 1539 participants)
- Compared to glatiramer acetate, there was no significant difference in reducing the number of patients with disability worsening for both dosages of dimethyl fumarate (high dosage:  $RR = 0.82$ , 95% CI 0.57 to 1.17,  $P = 0.27$ ; low dosage:  $RR = 0.82$ , 95%CI 0.57 to 1.17,  $P = 0.27$ ).

##### **The number of patients with at least one adverse event (AE) at two years of follow-up**

- Overall, compared with placebo group, the pooled results showed that the incidence of AEs excluding relapses was significantly increased by both dosages of dimethyl fumarate administration (high dosage:  $RR = 1.38$ , 95%CI 1.27 to 1.51,  $P < 0.00001$ ; two studies

1531 participants; low dosage: RR = 1.37, 95% CI 1.25 to 1.49, P < 0.00001; two studies  
1540 participants

- The most common AEs included flushing (high dosage: RR = 6.57, 95%CI 4.62 to 9.35, P < 0.00001; two studies 1531 participants; low dosage: RR = 8.01, 95% CI 5.66 to 11.34, P < 0.00001; two studies 1540 participants; upper abdominal pain (RR = 1.91, 95% CI 1.35 to 2.69, P = 0.0003; two studies 1531 participants and RR = 1.69, 95% CI 1.19 to 2.41, P = 0.004; two studies 1540 participants, respectively); nausea (RR= 1.59, 95% CI 1.19 to 2.12, P = 0.002); two studies 1531 participants and RR= 1.39, 95% CI 1.03 to 1.87, P = 0.03; two studies 1540 participants (respectively); diarrhoea (RR = 1.55, 95% CI 1.20 to 2.01, P = 0.0008); two studies 1531 participants and RR = 1.31, 95% CI 0.91 to 1.87, P = 0.14; two studies 1540 participants, respectively); and proteinuria (RR = 1.46, 95% CI 1.06 to 2.00, P = 0.02; two studies 1531 participants and RR = 1.14, 95% CI 0.81 to 1.59, P = 0.45; two studies 1540 participants (respectively).

#### **The number of patients with at least one SAE at two years of follow-up**

- The pooled risk of SAEs excluding relapses both in participants receiving high-dose and low-dose dimethyl fumarate was not higher than that in participants receiving placebo (RR = 1.07, 95% CI 0.75 to 1.53, P = 0.71; two studies 1531 participants and RR = 1.05, 95% CI 0.63 to 1.74, P = 0.87; two studies 1540 participants, respectively).

#### **The number of patients who discontinued study drug because of AEs at two years of follow-up**

- There was a significant difference in the number of patients who discontinued study drug because of AEs excluding relapses between participants receiving dimethyl fumarate and participants receiving placebo (high dosage: RR = 2.16 (95% CI 1.54 to 3.03, P < 0.00001); two studies 1531 participants; low dosage: RR = 2.18 (95% CI 1.56 to 3.06, P < 0.00001; two studies 1540 participants
- Overall, the incidences of study drug discontinuation due to adverse effects both in highdose group and low-dose group, such as diarrhoea (1.97% and 0.91%, respectively), flushing (1.58% and 3.12%, respectively), nausea (1.58% and 0.78%, respectively) and upper abdominal pain (1.32% and 0.78%, respectively) were low.

#### **The ARR at two years of follow-up**

- Compared to placebo, the pooled results showed both dosages of dimethyl fumarate significantly reduced the ARR at two years of follow-up (high dosage: rate ratio = 0.51, 95% CI 0.45 to 0.59, P < 0.00001; two studies 1532 participants; low dosage: rate ratio = 0.51, 95% CI 0.44 to 0.59, P < 0.00001; two studies 1540 participants).
- Compared to glatiramer acetate, there was a significant difference in reducing the ARR for both dosages (high dosage: rate ratio = 0.69, 95% CI 0.56 to 0.86, P = 0.0007; low dosage: rate ratio = 0.76, 95% CI 0.62 to 0.94, P = 0.01).

#### **Anmerkung/Fazit der Autoren**

There is moderate-quality evidence to support that dimethyl fumarate at a dose of 240 mg orally three times daily or twice daily reduces both on the number of patients with a relapse and the annualised relapse rate over two years of treatment. However, the quality of the evidence to support the benefit in reducing the number of patients with disability worsening is low. There is no high-quality data available to evaluate the benefit on MRI outcomes.

The common adverse effects (AEs) such as flushing and gastrointestinal events (e.g. diarrhoea, nausea, and upper abdominal pain) are mild-to-moderate for most of patients. Lymphopenia and leukopenia are uncommon AEs but significantly associated with dimethyl fumarate. Both dosages of dimethyl fumarate have similar benefit and safety profile, which supports the option of low-dose administration.

### 3.3 Systematische Reviews

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#### Tsivgoulis G et al., 2016 [27].

The Efficacy of Natalizumab versus Fingolimod for Patients with Relapsing-Remitting Multiple Sclerosis: A Systematic Review, Indirect Evidence from Randomized Placebo-Controlled Trials and Meta-Analysis of Observational Head-to-Head Trials.

#### Fragestellung

to compare the relative efficacy of Natalizumab and Fingolimod in RRMS patients by estimating an indirect effect using available randomized placebo-control trials and by estimating an effect from observational studies on the reported efficacy outcomes.

#### Methodik

##### Population:

- RRMS patients

##### Intervention/Komparator:

- RCT treatment arms with any of the two drugs (Natalizumab or Fingolimod) versus the corresponding placebo arms, and meta-analysis patients receiving Natalizumab versus those receiving Fingolimod in the included observational studies.

##### Endpunkte:

- ARR, percentage of patients with disability progression, percentage of patients who were free of relapses and percentage of patients with no evidence of disability progression (NEDA) during the study period

##### Recherche/Suchzeitraum:

- EDLINE, SCOPUS and the CENTRAL Register of Controlled Trials databases on April 16th, 2016

##### Qualitätsbewertung der Studien:

- Cochrane Handbook

#### Ergebnisse

##### Anzahl eingeschlossener Studien:

- 8 studies

**Table 1. Baseline characteristics of patients in the included Randomized Clinical Trials.**

	Natalizumab	Fingolimod	p-value
RCTs	AFFIRM [16]	FREEDOMS I [17], FREEDOMS II [18]	
Patients (n)	627	783	
Age (years±SD)	35.6±8.5	38.5±8.6	<0.001
Males (n, %)	178 (28%)	212 (27%)	0.675
Disease duration (median, years)	5.0	N/A	N/A
History of previous DMT	N/A*	43.2%	-
Relapses in previous year (mean±SD)	1.53±0.91	1.46±0.84	0.134
Baseline EDSS (mean±SD)	2.3±1.2	2.3±1.3	1.0
Gd+ lesions (mean±SD)	2.2±4.7	1.4±4.2	<0.001
≥9 T2-MRI lesions	597 (95%)	N/A	N/A

n: number, SD: standard deviation, DMT: disease modifying treatment, Gd+: gadolinium enhancing, N/A: not available

\*patients receiving treatment with cyclophosphamide or mitoxantrone within the previous year, or treatment with interferon beta, glatiramer acetate, cyclosporine, azathioprine, methotrexate, or intravenous immune globulin within the previous 6 months or treatment with interferon beta, glatiramer acetate, or both for more than six months were excluded.

#### Qualität der Studien:

- K.A.

#### Studienergebnisse:

Overall analysis and indirect estimates in randomized clinical trials

- Natalizumab was found to be associated with a greater reduction in the 2-year ARR compared to placebo (SMD: -0.62; 95% CI: from -0.76 to -0.48 and OR:0.32; 95%CI: from 0.25 to 0.41) than the ARR reduction of Fingolimod in 2 years compared to placebo (SMD: -0.38, 95% CI: from -0.48 to -0.28 and OR:0.50 95%CI: from 0.42 to 0.60)
- However, the percentage of patients with no relapse at 2 years was not found to be significantly different among the RRMS patients treated with Natalizumab and those treated with Fingolimod (OR for Natalizumab: 3.04, 95% CI: from 2.29 to 4.03 vs OR for Fingolimod: 2.54, 95% CI: from 2.05 to 3.17, p-value for subgroup differences:0.33; ORindirect:1.20, 95% CI: from 0.84 to 1.71).
- Similarly, the percentage of patients with disability progression at 2 years did not differ between RRMS patients treated with Natalizumab and Fingolimod (OR for Natalizumab: 0.51, 95% CI: from 0.37 to 0.70 vs OR for Fingolimod: 0.67, 95% CI: from 0.48 to 0.94, p-value for subgroup differences: 0.23, Fig C in S1 File; ORindirect: 0.76, 95% CI: from 0.48 to 1.21).
- Finally, a significantly higher percentage of RRMS with NEDA at 2-years was found in patients randomized to receive Natalizumab than those randomized to receive Fingolimod in the corresponding RCTs [8,23] (OR for Natalizumab: 7.42, 95%CI: from 4.66 to 11.81 vs OR for Fingolimod: 4.08, 95%CI: from 3.04 to 5.47, p-value for subgroup differences:0.03; ORindirect:1.82, 95% CI: from 1.05 to 3.15).

Overall and subgroup analyses in observational study data

- In the subsequent analysis of all available observational study data no significant difference ( $p= 0.66$ ) in the 2-year ARR was found among Natalizumab and Fingolimod (SMD:-0.05, 95% CI: from -0.26 to 0.16; and OR: 0.92; 95%CI: from 0.64 to 1.34;).
- Similarly, no significant difference in the proportion of patients with disability progression was observed between RRMS patients treated with Natalizumab and those treated with Fingolimod at both 1-year (OR: 1.37, 95% CI: from 0.95 to 1.98,  $p$  value = 0.10) and 2-years (OR: 1.08, 95% CI: from 0.77 to 1.52;  $p$ -value = 0.36)

- Finally, in another subgroup analysis patients treated with Natalizumab were found to have a significantly higher proportion of relapse-free patients at 2-years patients compared to those treated with Fingolimod (OR: 2.19, 95% CI: from 1.15 to 4.18, p-value = 0.02).
- However, this difference was marginally not significant during the first year (OR: 1.61, 95% CI: from 0.94 to 2.78, p-value = 0.09) and considerable heterogeneity was observed within studies for both the 1st and 2nd year ( $I^2 > 80\%$ ).

#### Anmerkung/Fazit der Autoren

Indirect analyses of RCT data and head-to-head comparisons of observational findings indicate that NTZ may be more effective than FGD in terms of disease activity reduction in patients with RRMS. However, head-to-head RCTs are required to independently confirm this preliminary observation.

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#### Siddiqui M et al., 2018 [24].

Systematic literature review and network meta-analysis of cladribine tablets versus alternative disease-modifying treatments for relapsing–remitting multiple sclerosis

#### Fragestellung

The aim of this analysis was to assess the comparative efficacy and safety of cladribine tablets versus alternative DMTs in patients with RRMS.

#### Methodik

##### Population:

- adult patients with RRMS, or a patient population with subgroup of  $\geq 80\%$  RRMS patients

##### Intervention:

- cladribine

##### Komparator:

- alternative DMTs

##### Endpunkte:

- efficacy and safety

##### Recherche/Suchzeitraum:

- Systematische Literaturrecherche bis Januar 2017

##### Qualitätsbewertung der Studien:

- risk of bias was assessed using National Institute for Health and Care Excellence (NICE), German Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG), and French Haute Autorité de Santé (HAS) checklists, and by study grade (for adequacy of concealment of allocation) and Jadad score (for study quality and study reporting)

##### NMA:

- methods of Dias et al.
- A Bayesian p-value of  $<.05$  was used to determine statistical significance.

## Ergebnisse

### Anzahl eingeschlossener Studien:

- 44 Studien

### Qualität der Studien:

- Across included studies, the risk of bias was generally low according to NICE, IQWiG and HAS checklists. Exceptions were the open-label study of IFN beta-1a 44 mcg versus IFN beta-1b49 and studies evaluating alemtuzumab, which were all single-, assessor-blinded and considered at higher risk of bias. Included studies were generally of good quality in terms of reporting, despite a notable absence of reporting on the clinical significance of study findings.

### Studienergebnisse:

#### Annualized relapse rate

- In patients with active RRMS, cladribine tablets were associated with a significant 58% reduction in ARR versus placebo ( $p<.05$ ); cladribine tablets were similar or significantly better than other DMT regimens and ranked fourth among DMTs, behind alemtuzumab, natalizumab and ocrelizumab.
- For CDP for 6 months and NEDA, improvements with cladribine tablets were significantly greater than those of placebo ( $p<.05$ ), with no comparator DMT demonstrating significantly better results.
- Similar findings were reported in the HRA+DAT population.
- Overall adverse event risk for cladribine tablets did not differ significantly from that of placebo and most alternative DMTs.

#### Anmerkung/Fazit der Autoren

This is the first NMA to consider recently approved treatments for RRMS, cladribine tablets, ocrelizumab and daclizumab. The results of this analysis show that cladribine tablets are a comparatively effective and safe alternative to other DMTs in both the active RRMS and HRA+DAT populations.

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#### Berardi A et al., 2019 [1].

Estimating the comparative efficacy of cladribine tablets versus alternative disease modifying treatments in active relapsing-remitting multiple sclerosis: adjusting for patient characteristics using meta-regression and matching-adjusted indirect treatment comparison approaches.

#### Fragestellung

A recent network meta-analysis by Siddiqui and colleagues suggested that cladribine tablets are a comparatively effective and safe alternative to other highly efficacious DMTs in both active RRMS and in the HDA subpopulation<sup>19</sup>. However, due to the limited amount of subpopulation data (e.g. in HDA, RES and SOT subpopulations) reported for comparator studies, it was not feasible to conduct a conventional mixed treatment or indirect treatment comparison (ITC) of cladribine tablets across all relevant comparators within these subpopulations. This is due to a lack of specific published comparator data (e.g. ocrelizumab), a lack of a common comparator link (e.g. alemtuzumab) or due to numbers being insufficient

to draw a robust informative comparison (e.g. fingolimod and natalizumab) 20. The difficulty of conducting an ITC is further highlighted in a recent network meta-analysis which, due to paucity of data, was only able to estimate fingolimod versus natalizumab in RES-RRMS and fingolimod versus dimethyl fumarate in HDA-RRMS20. Given the particular importance of early, efficacious interventions in reducing the progression of MS, it is critical to examine alternative methodological approaches to determine the comparative efficacy across a range of DMTs within these subpopulations of RRMS patients4,8.

To this end, a series of meta-regression models with adjustment for baseline risk were fitted to data from the intention to treat cohorts of trials identified in the systematic literature review conducted by Siddiqui and colleagues19. The primary objective of this study was to further estimate the comparative efficacy of cladribine tablets versus alternative DMTs in adult patients with active RRMS, including meta-regression to provide subpopulation-specific estimates of drug effect for all relevant comparators in all populations of interest and with a particular focus on the high-efficacy comparators, namely fingolimod, natalizumab, alemtuzumab and ocrelizumab. The secondary objective was to determine the feasibility of conducting a matching-adjusted indirect comparison (MAIC) employing patient-level data to validate the results from the meta-regression.

[19] Siddiqui MK, Khurana IS, Budhia S, et al. Systematic literature review and network meta-analysis of cladribine tablets versus alternative disease-modifying treatments for relapsing–remitting multiple sclerosis. Curr Med Res Opin. 2018;34:1361–1371.

[20] Huisman E, Papadimitropoulou K, Jarrett J, et al. Systematic literature review and network meta-analysis in highly active relapsing– remitting multiple sclerosis and rapidly evolving severe multiple sclerosis. BMJ Open. 2017;7:e013430.

## Methodik

- Siehe Siddiqui M et al., 2018 [24]

A Bayesian meta-regression analysis was conducted to provide HDA-, RES- and SOT-specific estimates of the relative effect of cladribine tablets compared to all relevant DMT comparators in patients with active RRMS. The focus of the present manuscript is on the key highly efficacious comparators of alemtuzumab, natalizumab, fingolimod and ocrelizumab. This was achieved by running a series of models with adjustment for baseline risk that were fitted to data from the intention to treat cohorts of trials identified in the SLR. The analysis was based on methodology for meta-regression on baseline risk published by the NICE Decision Support Unit (DSU)25. By modeling the effect of baseline risk on treatment effects relative to placebo, the regression model can be used to estimate the effects for any baseline risk characterizing a 1372 A. BERARDI ET AL. subpopulation (e.g. the average baseline risk corresponding to the RES or SOT subpopulations in the CLARITY trial). Baseline risk was defined as the probability of disability progression confirmed at 3 or 6 months (measured at 24 months) or the annualized relapse rate in the placebo arm. The baseline risk in non-placebo-controlled studies was estimated in the network based on the joint distribution of the available placebo-specific effects and estimated differences in relative treatment effects.

## Ergebnisse

### Anzahl eingeschlossener Studien:

- Siehe Siddiqui M et al., 2018 [24]

### Qualität der Studien:

- Siehe Siddiqui M et al., 2018 [24]

Studienergebnisse:

- Confirmed disability progression at 6 months
  - Only studies reporting 6M-CDP at 24 months were included in the analysis. The network for 6M-CDP consisted of 19 studies reporting outcomes for 14 treatments. Overall, 11 of the 19 studies were placebo-controlled trials and were directly informative to the baseline risk adjustment (centered on placebo).  
○ The results of the meta-regression analysis showed significant overlap in the credible intervals for the HRs of 6M-CDP, with no therapy statistically dominating in terms of efficacy  
○ At the point estimate level, cladribine tablets were predicted to be more efficacious in the HDA population than fingolimod (HR: 0.77, 95% CrI [0.40; 1.44]), alemtuzumab (HR: 0.92, 95% CrI [0.40; 2.23]) and ocrelizumab (HR: 0.87, 95% CrI [0.36; 2.02]). However, a similar result was not found for the comparison of cladribine tablets and natalizumab (HR: 1.08, 95% CrI [0.53; 2.21])  
○ Given the similarity in the baseline risk between the HAD and RES subpopulations, analogous HR estimates versus placebo were obtained in the HDA and RES subpopulations. All interventions in the SOT subpopulation were estimated to be less effective against placebo than in the HDA population due to the negative association of baseline risk on the relative treatment effect.
- Confirmed disability progression at 3 months
  - When studies reporting 3M-CDP at 24 months were included in the analysis, the network consisted of 18 studies reporting outcomes for 15 treatments. Overall, 13 of the 18 studies used in the meta-regression were placebo-controlled trials  
○ Similar to 6M-CDP, the results of the meta-regression analysis showed considerable overlap in the credible intervals for the HRs of 3M-CDP; no therapy statistically dominated in terms of efficacy  
○ At the point estimate level, cladribine tablets were predicted to have a similar efficacy profile to natalizumab in the HDA population (HR versus natalizumab of 0.97, 95% CrI [0.58; 1.63]). A similar result was not found for the comparison of cladribine tablets to alemtuzumab (HR: 1.72, 95% CrI [0.66; 4.67]) or ocrelizumab (HR: 1.15, 95% CrI [0.58; 2.24]); cladribine tablets were more efficacious than fingolimod (HR: 0.72, 95% CrI [0.46; 1.12]).
- Annualized relapse rate
  - A total of 41 studies covering 17 different treatments were included in the ARR network. Twenty-five of the 41 studies were placebo-controlled trials and were directly informative to the baseline risk adjustment  
○ Cladribine tablets, alemtuzumab, natalizumab, fingolimod and ocrelizumab were each estimated to reduce the ARR with very high probability, greater than 0.975, when compared to placebo in all subpopulations  
○ At the point estimate level, cladribine tablets were predicted to be more efficacious than fingolimod (rate ratio, RR: 0.89, 95% CrI [0.69; 1.14]), but less efficacious than alemtuzumab (RR: 1.20, 95% CrI [0.89; 1.63]), natalizumab (RR: 1.16, 95% CrI [0.89; 1.53]) and ocrelizumab (RR: 1.06, 95% CrI [0.78; 1.45]).

### Anmerkung/Fazit der Autoren

The results of the analysis showed significant overlap in the credible intervals for the HRs of confirmed disability progression at 3 and 6 months, with no therapy statistically dominating in terms of efficacy. Cladribine tablets were associated with a high probability of being superior to placebo in HDA, RES and SOT subpopulations. Consequently, the results of these meta-regression analyses suggest that cladribine tablets have comparable efficacy to alternative high-efficacy DMTs in active RRMS, specifically in patients diagnosed with HDA, RES or SOT. These findings also support the previous network meta-analysis that suggested cladribine tablets were a comparatively effective and safe alternative to other DMTs in RRMS patients with high disease activity.

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### McCool R et al., 2019 [18].

Systematic review and network meta-analysis comparing ocrelizumab with other treatments for relapsing multiple sclerosis.

### Fragestellung

The objective of this study was to conduct a systematic literature review (SLR) and NMA to evaluate the relative efficacy and safety of ocrelizumab compared with all approved DMTs for the treatment of patients with RMS, across seven measures of efficacy and safety.

### Methodik

#### Population:

- Adults. Patients with relapsing forms of MS. Trials of mixed populations more than 75% have a relapsing form of MS

#### Intervention:

- Ocrelizumab (600mg), Interferon β-1a (s.c. [22–44µg] or i.m. [30µg]), Interferon β-1b (250–500µg), PEGylated interferon (125mg), Glatiramer acetate (20mg, 40mg), Natalizumab (300mg), Teriflunomide (7 or 14mg), Fingolimod (0.5mg), Dimethyl fumarate (240mg), Daclizumab (150mg), Alemtuzumab (12mg), Cladribine (3.5 or 5.25mg/kg)

#### Komparator:

- Placebo or DMT

#### Endpunkte:

- Annualized relapse rate/number of relapses, 12-week CDP, 24-week CDP, Proportion relapse free, Serious adverse events, Discontinuations due to adverse events, All cause discontinuation

#### Recherche/Suchzeitraum:

- MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials were originally searched on 30 October 2014 to identify randomized controlled trials (RCTs) for inclusion in the review and network meta-analyses (NMA). updates performed in November 2016 and July 2017.

### Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool

### **Ergebnisse**

#### Anzahl eingeschlossener Studien:

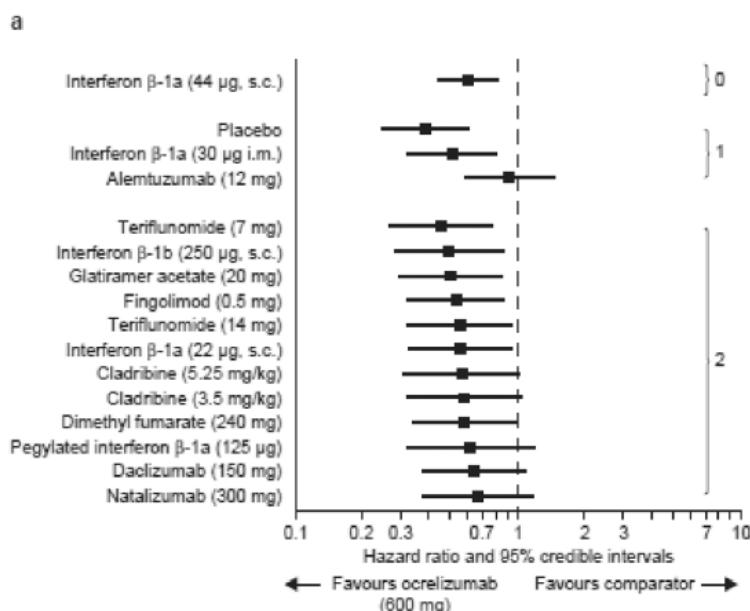
- 33 trials were included

#### Qualität der Studien:

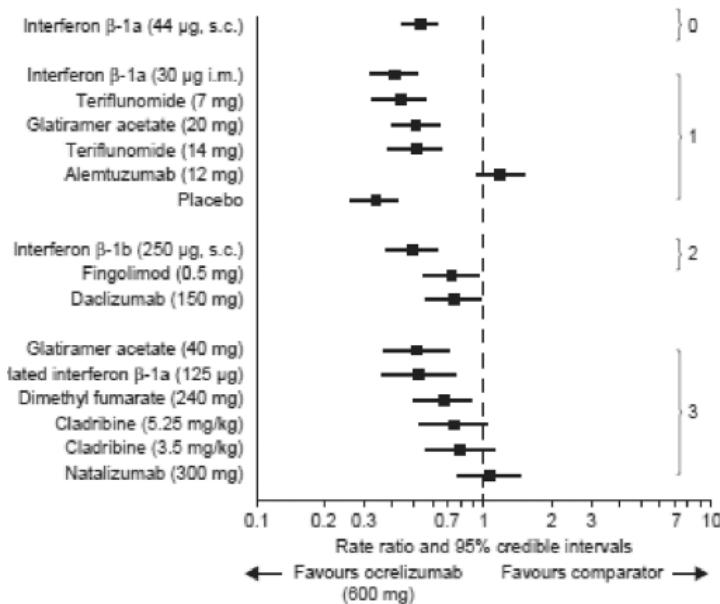
- The risk of bias in the 46 trials assessed was generally acceptable. There was little evidence to suggest that authors measured more outcomes than they reported. There is some risk of bias because some trials were not double-blind and had unexpected drop outs and missing or inappropriate ITT analyses. The risk of bias evaluation was limited by the availability of information for each of the trials.

#### Studienergebnisse:

- 12-week confirmed disability progression network
  - Comparisons of ocrelizumab versus other DMTs provided evidence that ocrelizumab was more effective in reducing the risk of 12-week CDP than 10 other treatments, including placebo



- Annualized relapse rate network
  - Comparisons of ocrelizumab versus other DMTs provided evidence that ocrelizumab was more effective in reducing the ARR than 12 other treatments, including placebo



- Serious adverse events network
  - Comparisons of ocrelizumab versus other DMTs showed that there was no evidence of a difference between ocrelizumab and any other treatments in the risk of SAEs
- 24-week CDP
  - Comparisons of ocrelizumab versus other DMTs provided evidence that ocrelizumab was more effective in reducing the risk of 24-week CDP than placebo, interferon β-1a 44 µg (Rebif) and teriflunomide 7 mg
- all-cause discontinuation
  - For all-cause discontinuation of treatment, the comparison of 17 treatments in 26 trials (Table D17) provided evidence to suggest that patients who receive ocrelizumab are less likely to discontinue than patients who receive pegylated interferon β-1a or interferon β-1a 44 µg (Rebif), but are more likely to discontinue than patients who receive alemtuzumab or natalizumab

#### Anmerkung/Fazit der Autoren

Ocrelizumab has proven efficacy versus interferon β-1a 44 µg (Rebif) in the pivotal trials OPERA I and OPERA II (Hauser et al., 2017). However, direct comparisons of ocrelizumab with all other DMTs have not been conducted. Therefore, we estimated relative treatment effects for ocrelizumab versus all DMTs currently approved for the treatment of RMS, by examining four efficacy and three safety outcomes in NMAs. These models and the SUCRA ranking values calculated from them suggest that ocrelizumab has an efficacy and safety profile that is superior to or comparable with other available DMTs across all outcomes, except natalizumab and alemtuzumab for one safety outcome: all-cause discontinuation. When interpreting these all-cause discontinuation results, it is necessary to consider possible bias from the inability to discontinue induction treatments once the induction phase has been completed, and the fact that patients were not blinded to the treatment in some pivotal open-label trials. Ocrelizumab provides a treatment option that demonstrates consistent efficacy and safety across all analyzed outcomes.

Most recently in November 2017, Siddiqui et al. compared efficacy across five outcomes: ARR, 12-week CDP, 24-week CDP, proportion relapse-free, no evidence of disease activity (NEDA) and a single combined safety outcome (any AEs) (Siddiqui et al., 2017). These analyses were performed in active relapsing-remitting MS (RRMS) and a subgroup with high disease activity. This manuscript made different analysis assumptions, including the inclusion of trials with a shorter duration in the ARR network but the exclusion of trials under 24 months from the CDP NMAs; they also ran an NMA on the NEDA endpoint despite differences in imaging definitions and monitoring timepoints across trials. In addition, the treatment rankings in Siddiqui et al. were based on the point estimates of treatment effect in the NMAs, which, unlike the SUCRA approach reported here, do not consider the uncertainty of these ranking estimates.

#### *Kommentare zum Review*

Analysis for this work was performed by F. Hoffmann-La Roche Ltd., Quantics Biostatistics and York Health Economics Consortium (YHEC) and funded by F. Hoffmann-La Roche Ltd. Medical writing support was provided by Fraser Harris of Oxford PharmaGenesis, UK, with funding from F. Hoffmann-La Roche Ltd.

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#### **Huisman E et al., 2017 [13].**

Systematic literature review and network meta-analysis in highly active relapsing-remitting multiple sclerosis and rapidly evolving severe multiple sclerosis

#### **Fragestellung**

The objectives of this study were to conduct a SLR (systematic literature review) and to assess the feasibility of conducting a Bayesian NMA to evaluate the relative efficacy and safety of DMTs in patients with highly active (HA) or rapidly evolving severe (RES).

#### **Methodik**

##### Population:

- Adults with HA RRMS or RES RRMS

##### Intervention:

- Fingolimod, Beta interferon, Glatiramer acetate, Natalizumab, Teriflunomide, Dimethyl fumarate, Alemtuzumab

##### Komparator:

- Any of the interventions above or best supportive care

##### Endpunkte:

- Functional Outcomes: Annualized relapse rate (ARR), ARR ratio, Hazard ratio (HR) for time to relapse, HR for disability progression (at 3 and 6 months or otherwise), Proportion of patients with no relapses, Mean change from baseline in EDSS score, Proportion of patients disease activity free, Proportion of patients with no change in EDSS; MRI Outcomes: Mean number of new or enlarged T2 hyper intense lesions, Proportion of patients with no T2 lesions, Mean MS Functional composite scale z-score

#### Recherche/Suchzeitraum:

- November 2014

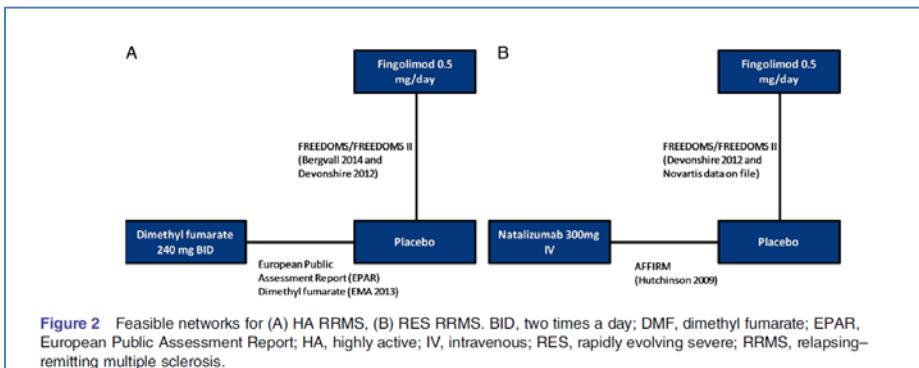
#### Qualitätsbewertung der Studien:

- Qualitätsbewertung der Studien: National Institute for Health and Care Excellence (NICE) critical assessment checklist

#### **Ergebnisse**

##### Anzahl eingeschlossener Studien:

- 8 RCTs
- The studies included were all post hoc subgroup analyses of double-blind, parallel-group, multicentre phase III RCTs.
- HA RRMS (N=4) and RES RRMS (N=3) or both separately (N=1)
- The subgroup analysis for natalizumab reported on one RCT (AFFIRM), whereas fingolimod and DMF were supported by pooled analysis of two studies (FREEDOMS/FREEDOMS II and DEFINE/ CONFIRM, respectively).



#### Qualität der Studien:

- Many items of the risk of bias assessment were not well reported and therefore the risk of bias of the included subgroup analyses is unclear.

#### Studienergebnisse:

- HA RRMS: no statistically significant difference between fingolimod and DMF on ARR and disability progression; mean rate ratio of 0.91 (95% CrI 0.57, 1.47) and HR of 0.55 (95% CrI 0.21, 1.12), respectively.
- RES RRMS: no statistically significant difference was found for the comparison of fingolimod with natalizumab for ARR and disability progression (3-month and 6-month confirmed); mean rate ratio of 1.72 (95% CrI 0.84, 3.52) and HR of 1.62 (95% CrI 0.51, 5.13) for 3-month confirmed disability progression and 1.86 (95% CrI 0.49, 7.12) for 6-month confirmed disability progression, respectively.
- NMA: it was not possible to evaluate whether direct and indirect evidence were in agreement in closed loops.

### Anmerkung/Fazit der Autoren

Data limitations are apparent when conducting an informative indirect comparison for the HA and RES RRMS subgroups as the subgroups analyses were retrospective analyses of studies powered to indicate differences across entire study populations. Comparisons across treatments in HA or RES RRMS will be associated with high levels of uncertainty until new data are collected for these subgroups.

### Kommentare zum Review

- It should also be noted that all included studies were post hoc subgroup analyses of large randomised trials, which were not powered to detect a statistically significant difference between interventions in the HA or RES RRMS subgroups.
- Keine Angaben ob es sich hierbei um therapienaiive Patienten oder vorbehandelte Patienten handelt.

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### Fogarty E et al., 2016 [2].

Comparative efficacy of disease-modifying therapies for patients with relapsing remitting multiple sclerosis: Systematic review and network meta-analysis

### Fragestellung

To perform a systematic review and network meta-analysis to evaluate the comparative efficacy of available therapies in reducing relapses and disability progression in RRMS.

### Methodik

→ The network meta-analysis was conducted using Bayesian Markov Chain Monte Carlo methods

#### Population:

- Adult patients with >90% RRMS (Some studies, while specifying RRMS as an inclusion criterion, also recruited a small number of patients with progressive disease. In these cases, studies which included >10% progressive patients were excluded)

#### Intervention:

- DMTs (interferon beta-1b (IFN β-1b) subcutaneous (SC) 250 mcg, IFN β-1a SC 22 mcg and IFN β-1a SC 44 mcg, IFN β-1a intramuscular (IM) 30 mcg, pegylated IFN β-1a SC 125 mcg, glatiramer acetate 20 mg, glatiramer acetate 40 mg, natalizumab, alemtuzumab, fingolimod, teri- flunomide, and dimethyl fumarate.

#### Komparator:

- DMT for RRMS as outlined in “interventions”; placebo

#### Endpunkte:

- Annualised relapse rate (ARR), disability progression

#### Recherche/Suchzeitraum:

- März 2016

### Qualitätsbewertung der Studien:

- Collaboration's Risk of bias tool

### **Ergebnisse**

#### Anzahl eingeschlossener Studien:

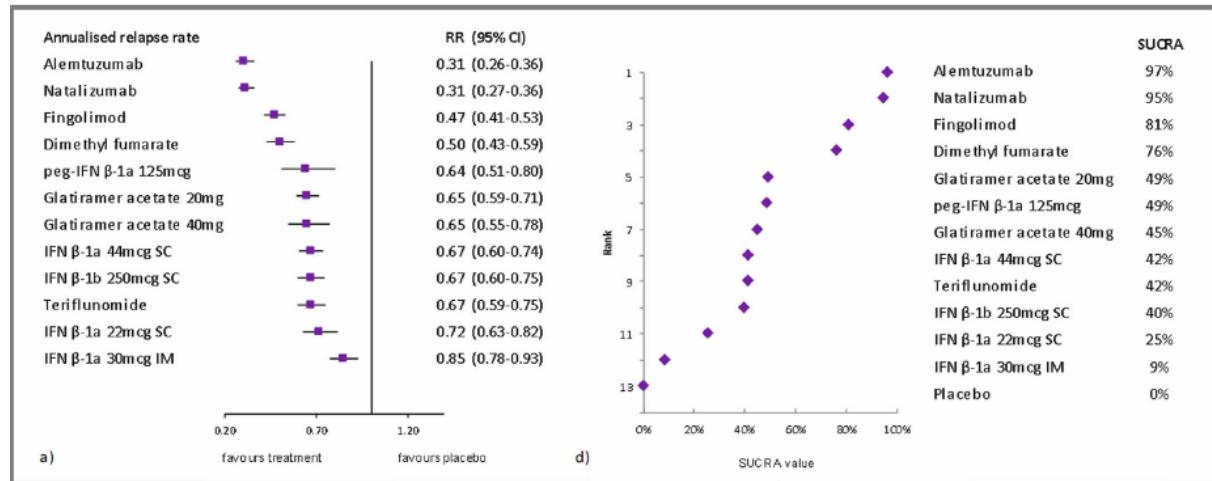
- 28 (N=17,040 patients)
- Eingeschlossenen Studien: ARR outcomes were obtain from all 28 trials, while data on disability progression confirmed after three months and six months were available from 16 trials.

#### Qualität der Studien:

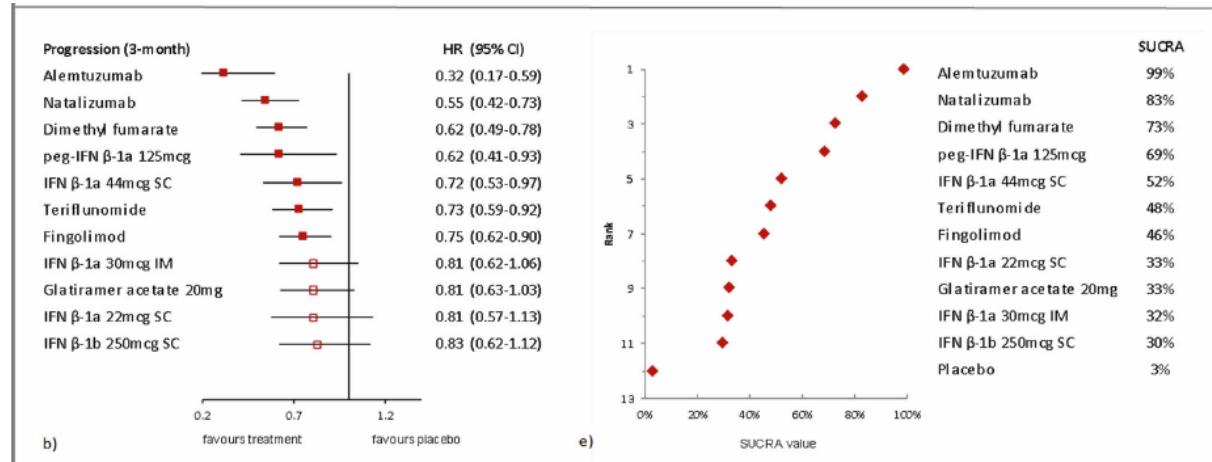
- The overall risk of bias within included studies was judged to be low in 14 studies (50%), medium in one study (4%) and high in 13 studies (46%).

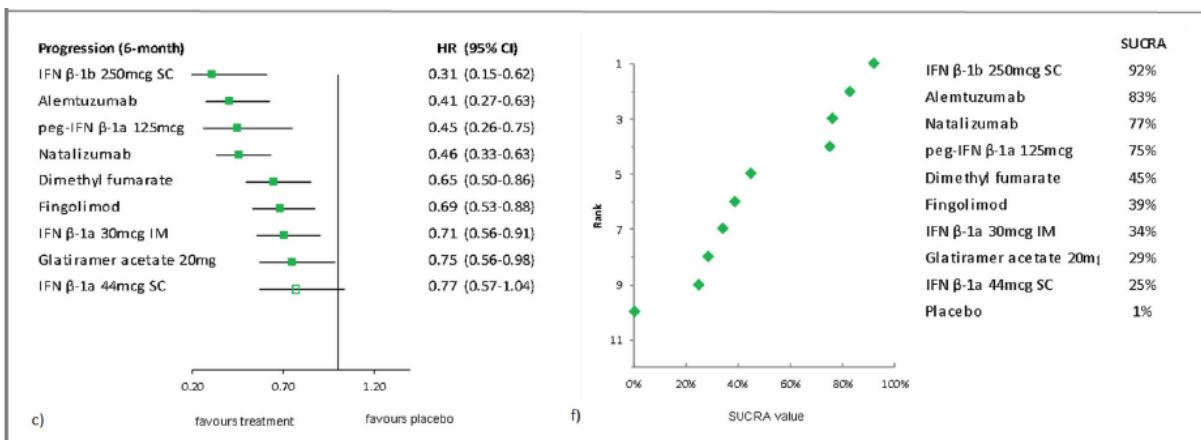
#### Studienergebnisse:

- Forest plots of treatments versus placebo and Network ranking for a) Annualised relapse rate



- Forest plots of treatments versus placebo and Network ranking for b) Disability progression confirmed at three months c) Disability progression confirmed at six months





### Anmerkung/Fazit der Autoren

Generally, DMTs were superior to placebo in reducing MS relapse rates and disability progression. However the magnitude of the reduction and the uncertainty associated with treatment effects varied between DMTs, and between the different outcomes included in the analysis, leading to variation in the relative ranking of treatments. The monoclonal antibody therapies alemtuzumab and natalizumab were generally among the highest ranked treatments for all outcomes. Among the oral therapies, fingolimod and dimethyl fumarate ranked higher than other therapies for ARR, while there was little difference between teriflunomide and other first-line DMTs for this outcome. Dimethyl fumarate, pegylated IFN β and IFN β 44 mcg occupied higher rankings than other DMTs for disability progression confirmed after three months and there was little to distinguish between the rankings of other treatments.

### Kommentare zum Review

- Keine Angaben ob es sich hierbei um therapienaiive Patienten oder vorbehandelte Patienten handelt.

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### Xu X et al., 2018 [28].

Efficacy and safety of monoclonal antibody therapies for relapsing remitting multiple sclerosis: A network meta-analysis

### Fragestellung

to investigate the relative efficacy and safety of existing monoclonal antibody therapies in treating RRMS.

### Methodik

#### Population:

- Patients with RRMS

#### Intervention

- natalizumab, alemtuzumab, daclizumab, and ocrelizumab.

Komparator:

- control arm could be any of the above listed biological therapies, INF $\beta$ -1a or placebo

Endpunkte:

- Primary outcomes: annualized relapse rate, proportion of patients exhibiting any serious adverse events
- Secondary outcomes: percentage of patients with no relapse, incidence of patients with new or enlarging hyperintense lesions on T2-weighted brain MRI, proportion of patients with any type of adverse events, and incidence rate of discontinuation due to adverse events.

Recherche/Suchzeitraum:

- PubMed, Embase, and the Cochrane Library up until September 15, 2017

Qualitätsbewertung der Studien:

- Cochrane Collaboration's risk of bias assessment tool

**Ergebnisse**

Anzahl eingeschlossener Studien:

- 13 eligible articles of 14 RCTs containing 9412 participants with RRMS
- INF $\beta$ -1a was the most common comparison treatment and no direct active comparisons between biologics had been performed. The 7 treatment regimens included in this network meta-analysis were natalizumab, natalizumab plus INF $\beta$ -1a, alemtuzumab, daclizumab, ocrelizumab, placebo, and INF $\beta$ -1a. As a standard treatment, INF $\beta$ -1a was compared against all the other 6 regimens. Twelve studies containing 8259 participants evaluated annualized relapse rate while 14 studies including 9412 participants reported incidence rate of serious adverse events.

Charakteristika der Population:

- mean age of included participants was 37.2 years old, the mean baseline EDSS score was 2.7, and the mean number of relapses in past year was 1.5.

Qualität der Studien:

- The risk of bias varied across individual studies, ranging from low to high. There were generally low risks of selection bias, detection bias, attrition bias, and reporting bias. The performance bias was moderate.

Studienergebnisse:

- ARR: On the whole, patients treated with INF $\beta$ -1a had an annualized relapse rate of 45.3%. Our results demonstrated that biological treatments (natalizumab, natalizumab plus INF $\beta$ -1a, alemtuzumab, daclizumab, and ocrelizumab) were associated with a significantly lowered risk of annualized relapse rate compared with INF $\beta$ -1a (RR 0.14 [95% CI 0.11–0.19] for natalizumab plus INF $\beta$ -1a, 0.31 [0.24–0.39] for alemtuzumab, 0.41 [0.26–0.64] for natalizumab, 0.45 [0.37–0.55] for daclizumab, and 0.45 [0.36–0.56] for ocrelizumab; Fig. 3a).

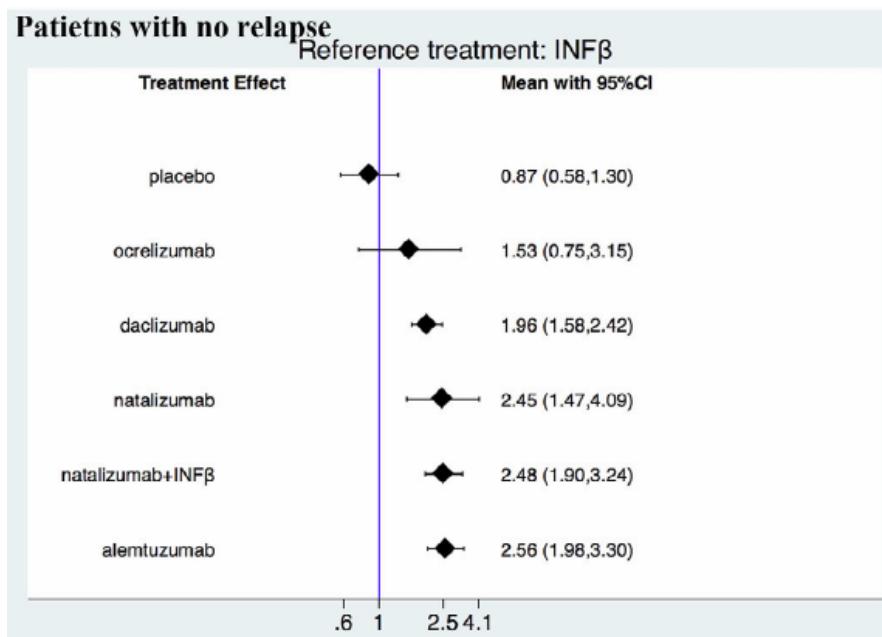
The rankograms (probability-based rankings) showed natalizumab plus INF $\beta$ -1a performed best in terms of decreasing annualized relapse rate, followed by alemtuzumab, natalizumab, daclizumab, ocrelizumab, INF $\beta$ -1a, and placebo.

- Serious adverse events: The total incidence rate of serious adverse events was 17.6% (1659/9412) across all included studies. In terms of serious adverse events, all biological treatments had similar incidence rate, except that placebo had a tendency of more serious adverse events.

Multiple sclerosis relapse that did not correspond to relapse tally for efficacy endpoints was also regarded serious adverse event and serious adverse events were more frequent in patients receiving placebo than in those receiving monoclonal antibodies or INF $\beta$ -1a were largely due to hospitalizations for treatment of relapses of multiple sclerosis.

The cluster ranking plot showed that natalizumab plus INF $\beta$ -1a was the regimen associated with the lowest risks of annualized relapse as well as serious adverse events. In terms of single-drug treatment, alemtuzumab was the monoclonal antibody that performed the best.

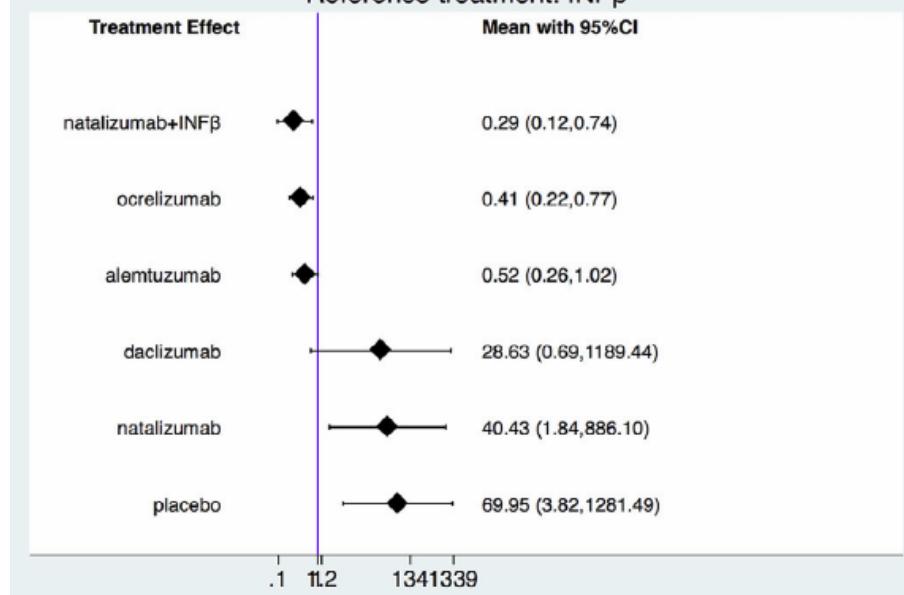
- Secondary outcomes:
  - Patients receiving monoclonal antibodies had significantly more chances of being free from relapse during study compared with INF $\beta$ -1a or placebo



- Interestingly, participants treated with daclizumab or natalizumab had higher risk of occurring new or enlarging T2 lesions compared with INF $\beta$ -1a (RR 28.63 [95% CI 0.69–1189.44] for daclizumab, and 40.43 [1.84–886.10] for natalizumab).

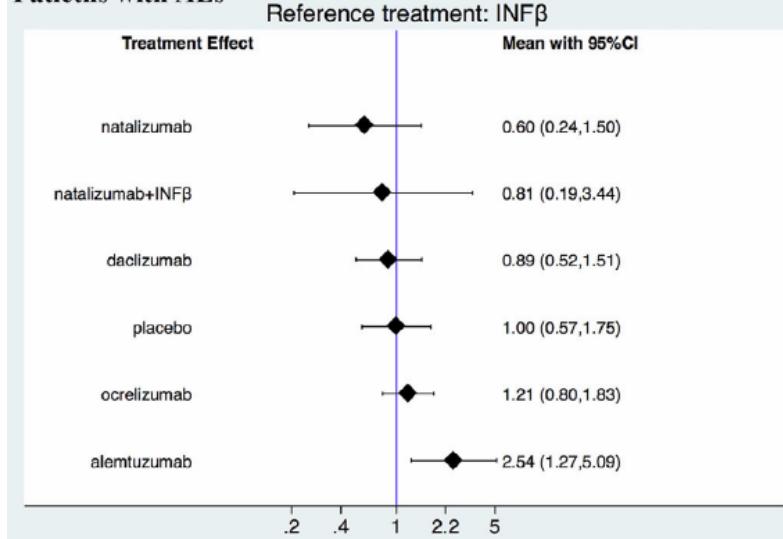
### Patients with new or enlarging T2 lesions

Reference treatment: INF $\beta$

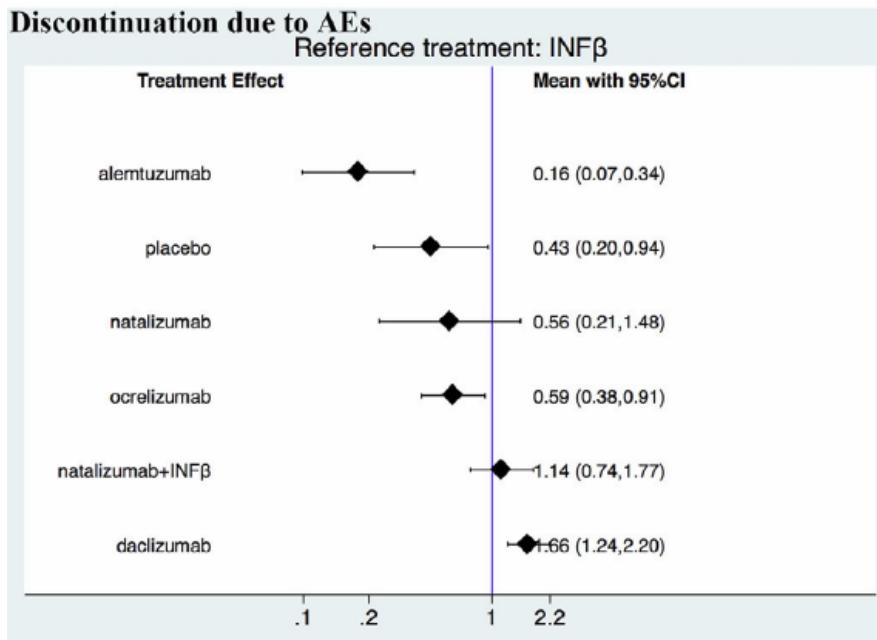


- Our analysis showed that most treatment regimens carried similar risks of adverse events except for alemtuzumab, which had a significant higher risk (RR 2.54 [95% CI 1.27–5.09]).

### Patients with AEs



- Alemtuzumab was associated with the lowest risk of discontinuations due to adverse events, with RR 0.16 (95% CI 0.07–0.34; Fig. 5d). The reason for this contradictory result of alemtuzumab might be that patients in all 3 studies comparing alemtuzumab with INF $\beta$ -1a received 1 g per day of intravenous methylprednisolone on 3 consecutive days at baseline and month 12 and the overall rate of discontinuation due to adverse events was very low. The rankograms of secondary outcomes



### Anmerkung/Fazit der Autoren

To conclude, our network meta-analysis provided a comprehensive summary of efficacy and safety of monoclonal antibodies for RRMS, which might provide a reference for the treatment. The results suggested that all 4 monoclonal antibodies exhibited a higher efficacy than INF $\beta$ -1a. Natalizumab plus INF $\beta$ -1a and alemtuzumab offered both high efficacy in terms of reducing relapse and low risk of serious adverse events. More direct comparison studies are warranted.

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**Lucchetta R et al., 2018 [17].**

Disease- Modifying Therapies for Relapsing–Remitting Multiple Sclerosis: A Network Meta- Analysis

### Fragestellung

to conduct a network meta-analysis of randomised clinical trials (RCTs) to provide evidence-based hierarchies of the efficacy and safety of all available DMTs for patients with RRMS.

### Methodik

#### Population:

- adults diagnosed with RRMS

#### Intervention/Komparator:

- traditional DMTs compared with the recently developed DMTs (The searched DMT therapies alemtuzumab, azathioprine; cladribine; daclizumab; dimethyl fumarate; fingolimod; glatiramer acetate; interferon  $\beta$ -1a; interferon  $\beta$ -1b; pegylated interferon; natalizumab; ocrelizumab; rituximab; teriflunomide

#### Endpunkte:

- annualised relapse rate (ARR), disability progression confirmed at 12 weeks (DPC12), disability progression confirmed at 24 weeks (DPC24), disability improvement confirmed at 12 weeks (DIC12), disability improvement confirmed at 24 weeks (DIC24), discontinuations due to adverse events (DAE) and change in QoL evaluated through Short Form-36 items or 12 items (SF-36 or SF-12)

#### Recherche/Suchzeitraum:

- in the PubMed and Scopus databases without any time limit or language restriction (updated in May 2017).

#### Qualitätsbewertung der Studien:

- GRADE

### **Ergebnisse**

#### Anzahl eingeschlossener Studien:

- 33 studies (29,150 participants)
- Eight studies included only treatment-naïve participants, and one study assessed only treatment-experienced patients; 16 studies included both treatment-naïve and treatment-experienced patients, and 15 articles did not report this information.
- 16 clinical trials comparing active therapies (head-to-head trials), 14 comparing different doses of DMT and 10 evaluating the active treatment against placebo.
- No study evaluating azathioprine or rituximab fulfilled the inclusion criteria and could be included in the systematic review.

#### Qualität der Studien:

- The outcomes more frequently associated with 'low risk of bias' were disability improvement and disability progression confirmed at 12 weeks; 'some concerns' appear more frequently in disability progression confirmed at 24 weeks, whereas 'high risk' was associated with QoL and ARR outcomes. The two domains more frequently scored as 'high risk of bias' were measurement of the outcome (due to the lack of masking of the assessors) and domain referring to missing outcome data.

#### Studienergebnisse:

- The most effective therapies for the outcome of annualized relapse rate were alemtuzumab (96% probability), natalizumab (96%) and ocrelizumab (85%), compared with all other therapies (hazard ratio versus placebo, 0.31, 0.31 and 0.37, respectively;  $p < 0.05$  for all comparisons) (high-quality evidence). However, no significant differences among these three therapies were found.

Discontinuation due to adverse events revealed similarity across all therapies, except for alemtuzumab, which showed less discontinuation when compared with interferon-1a intramuscular (relative risk 0.37;  $p < 0.05$ ).

#### **Anmerkung/Fazit der Autoren**

High-quality evidence shows that alemtuzumab, natalizumab and ocrelizumab present the highest efficacy among DMTs, and other meta-analyses are required to evaluate the

frequency of adverse events to better understand the safety profile of these therapies. Based on efficacy profile, guidelines should considerer a three-category classification (i.e. high, intermediate and low efficacy). Specific studies should be conducted for a more precise selection of therapies for more aggressive RRMS conditions.

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**Li H et al., 2019 [16].**

Comparative efficacy and acceptability of disease-modifying therapies in patients with relapsing-remitting multiple sclerosis: a systematic review and network meta-analysis.

### **Fragestellung**

In the present study, we performed a systematic review and network meta-analysis (NMA) to compare the efficacy and acceptability of DMTs in patients with relapsing–remitting MS

### **Methodik**

#### Population:

- patients of any gender and age with RRMS

#### Intervention:

- DMT (interferon beta-1b (Betaseron), interferon beta-1a (Avonex), glatiramer acetate, mitoxantrone, interferon beta-1a (Rebif), natalizumab, fingolimod, teriflunomide, dimethyl fumarate, peginterferon beta-1a (Plegridy), alemtuzumab and ocrelizumab.)

#### Komparator:

- Placebo or other DMT

#### Endpunkte:

- Our primary outcomes were efficacy (relapse rate measured by the total number of participants who experience at least one relapse over 24 months) and acceptability (treatment discontinuation measured by the number of participants who withdrew due to adverse events over 24 months). The secondary outcome was the number of participants whose disability worsened over 24 months, defined as an increase of at least 1.5 points on the EDSS scale for participants with a baseline score of 0, of at least 1.0 point for participants with a baseline score of 1.0 or more, and of at least 0.5 point for participants with a baseline score of 5.5 or more, sustained for 3 or 6 months

#### Recherche/Suchzeitraum:

- Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (PubMed), Embase (Embase.com), ClinicalTrials.gov ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)) and the World Health Organization (WHO) International Clinical Trials Registry Platform ([apps.who.int/trialsearch](http://apps.who.int/trialsearch)) for randomized controlled trials (RCTs) published from the date of database inception to Oct 31, 2018

#### Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool
- GRADE

## Ergebnisse

### Anzahl eingeschlossener Studien:

- Twenty-three studies reported between 1987 and 2018 with 14,096 participants were included in the analysis

### Charakteristika der Population:

- All trials reported full clinical and demographic characteristics, and approximately 70% of the sample population was female (9911 of 14,096). The mean age of the participants ranged from 18 to 55. The mean EDSS of the participants ranged from 0 to 5.0. Nineteen (82.6%) studies were funded by pharmaceutical companies.

### Studienergebnisse:

- relapse rate measured by the total number of participants who experience at least one relapse over 24 months
  - Direct comparison: Mitoxantrone, natalizumab, fingolimod, peginterferon beta-1a (Plegridy), dimethyl fumarate, teriflunomide, interferon beta-1a (Rebif), interferon beta-1a (Avonex), glatiramer acetate and interferon beta-1b (Betaseron) were statistically more efficacious than placebo in the efficacy outcome. Alemtuzumab and ocrelizumab were superior to interferon beta-1a (Rebif), and IFN β-1b (Betaseron) was better than IFN β-1b (Avonex).
  - NMA: In terms of efficacy, all drugs were more effective than placebo, with RRs ranging between 0.47 [95% credible interval (CrI) 0.27–0.80] for mitoxantrone and 0.87 (0.77–0.98) for IFN β-1a (Avonex). For the other comparison between drugs, alemtuzumab, ocrelizumab and natalizumab were more effective than the other drugs were (RRs ranging between 0.56 and 0.79), fingolimod (RRs ranging between 0.65 and 0.73), and peginterferon beta-1a and dimethyl fumarate (RRs ranging between 0.72 and 0.81). Teriflunomide, glatiramer acetate, IFN β-1a (Rebif), IFN β-1b (Betaseron) and IFN β-1a (Avonex) were among the least efficacious drugs (RRs ranging between 1.23 and 1.79). Mitoxantrone was more effective than teriflunomide (7 mg) and IFN β-1a (Avonex) (RRs ranging between 0.54 and 0.56).
- number of participants whose disability worsened over 24 months
  - Direct comparison: For sustained accumulation of disability (3 months), natalizumab, dimethyl fumarate, peginterferon beta-1a, IFN β-1a (Rebif), teriflunomide 14 mg and fingolimod were statistically better than placebo, and alemtuzumab and ocrelizumab were statistically better than IFN β-1a (Rebif). For sustained accumulation of disability (6 months), peginterferon beta-1a, IFN β-1a (Avonex) and fingolimod were statistically better than placebo, and alemtuzumab and ocrelizumab were statistically better than IFN β-1a (Rebif); IFN β-1b (Betaseron) was statistically better than IFN β-1a (Avonex).
  - NMA: In terms of sustained (3-month) disability progression, most of the DMTs were better than placebo was, except teriflunomide (7 mg), IFN β-1b (Avonex), glatiramer acetate and IFN β-1b (Betaseron). Alemtuzumab and ocrelizumab were better than other DMTs, apart from natalizumab and dimethyl fumarate. Natalizumab was better than glatiramer acetate and IFN β-1b (Betaseron). No usable data were available for mitoxantrone.
- Acceptability (treatment discontinuation)

- Direct comparison: For acceptability, IFN β-1b (Betaseron), IFN β-1a (Rebif), peginterferon beta-1a, dimethyl fumarate and glatiramer acetate were not as well tolerated as placebo; IFN β-1a (Rebif) was not as well tolerated as alemtuzumab.
- NMA: Glatiramer acetate, dimethyl fumarate, peginterferon beta-1a and IFN β-1a (Rebif) were worse than placebo (RRs ranging between 2.44 and 3.49). Fingolimod and IFN β-1a (Avonex) had significantly lower discontinuation than glatiramer acetate, dimethyl fumarate, peginterferon beta-1a and IFN β-1a (Rebif) (RRs ranging between 2.70 and 3.90). IFN β-1a (Rebif) was worse than alemtuzumab (RR 2.67).
- Safety (SAE)
  - For safety outcomes, there was no statistical significance between DMTs and placebo.
- SUCRA
  - The cluster rank plot (Fig. 2) shows that alemtuzumab, ocrelizumab, natalizumab and fingolimod are the regimens associated with not only the lowest risks of relapse rate but also the treatment discontinuation due to adverse events.

### Anmerkung/Fazit der Autoren

Our systematic review and network meta-analysis provide evidence-based hierarchies for the efficacy and acceptability of DMTs for RRMS, overcoming the major limitation of conventional pairwise meta-analyses. The results suggest that all DMTs were superior to placebo in reducing the relapse rate during the 2 years of follow-up, which corresponds to the pairwise meta-analyses. As to the comparison between drugs, three monoclonal antibodies, alemtuzumab, ocrelizumab and natalizumab were significantly better than other drugs; next was fingolimod, followed by peginterferon beta-1a and dimethyl fumarate. The traditional first-line drugs ( $\beta$ -interferons and glatiramer acetate) had few advantages in efficacy. Through the results of the NMA, we suggest that DMTs can be divided into three broad classes: drug of low efficacy, including  $\beta$ -interferons, glatiramer acetate and teriflunomide; drugs of moderate efficacy, including fingolimod, peginterferon beta-1a and dimethyl fumarate; and drugs of high efficacy, alemtuzumab, ocrelizumab and natalizumab. Although mitoxantrone ranked high in the SUCRA, the sample size of the related trial was too small and more research is needed to confirm its efficacy.

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### Tolley K et al., 2015 [25].

A Network Meta-Analysis of Efficacy and Evaluation of Safety of Subcutaneous Pegylated Interferon Beta-1a versus Other Injectable Therapies for the Treatment of Relapsing-Remitting Multiple Sclerosis

### Fragestellung

To evaluate the relative efficacy and safety of peginterferon beta-1a compared to other injectable DMTs approved for the treatment of RRMS

### Methodik

#### Population:

- RRMS or a patient population with a subgroup composed of >80% of patients with RRMS

Intervention:

- peginterferon beta-1a 125 µg every 2 weeks

Komparator:

- IFN beta-1a 30 µg QW, IFN beta-1b 250 µg every other day (EOD), IFN beta-1a 22 µg three times a week (TIW), IFN beta-1a 44 µg TIW, GA 20mg OD or placebo

Endpunkte:

- ARR (measured at study endpoint), CDP3M and CDP6M (including onset of disability progression at the end of the randomized phase of the trials). Safety: most common AEs ( $\geq 5\%$  incidence in any treatment group), annual incidence of any AEs or serious AEs

Recherche/Suchzeitraum:

- bis 2014 (Articles were limited to those published in English)

Qualitätsbewertung der Studien:

- Jadad Score

## Ergebnisse

Anzahl eingeschlossener Studien:

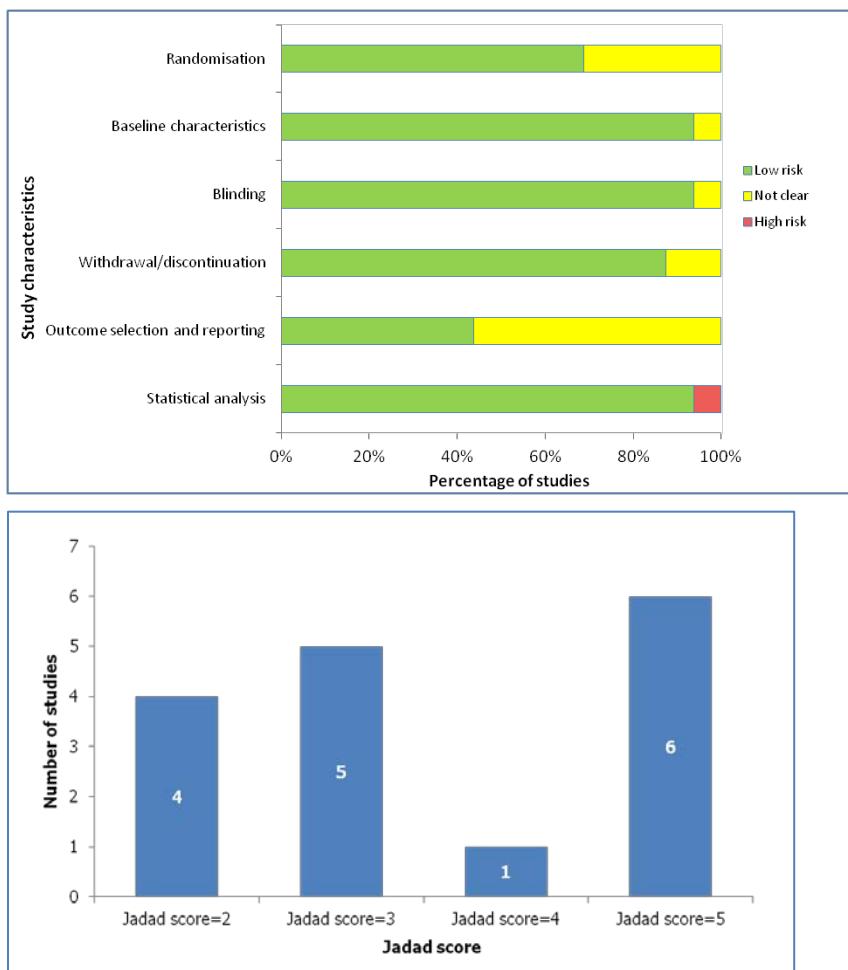
- 16 RCTs

Charakteristika der Population:

- Baseline patient characteristics were similar across trials and treatments. The mean age across trials ranged from 29–39 years, and the majority of participants were female and Caucasian. There were variations in the mean disease duration across trials, with values ranging from 1–8.3 years.
- Similarly, there were variations in the definition of relapse across trials, particularly the duration of symptoms.
- Of the 16 trials included in the analysis, nine defined relapse as the appearance of a new neurological symptom or worsening of an old symptom lasting at least 24 hours. Five trials required a duration lasting at least 48 hours, and two trials did not specify the duration.

Qualität der Studien:

- In terms of quality assessment, all 16 trials were randomized, but only 11 trials reported the randomization method and treatment allocation concealment. The majority of trials (15 of 16) were blinded appropriately to avoid detection bias, and there were no major imbalances in the baseline characteristics of the treatment groups. All but one trial analyzed outcomes on an intention- to-treat basis.



### Studienergebnisse:

- ARR

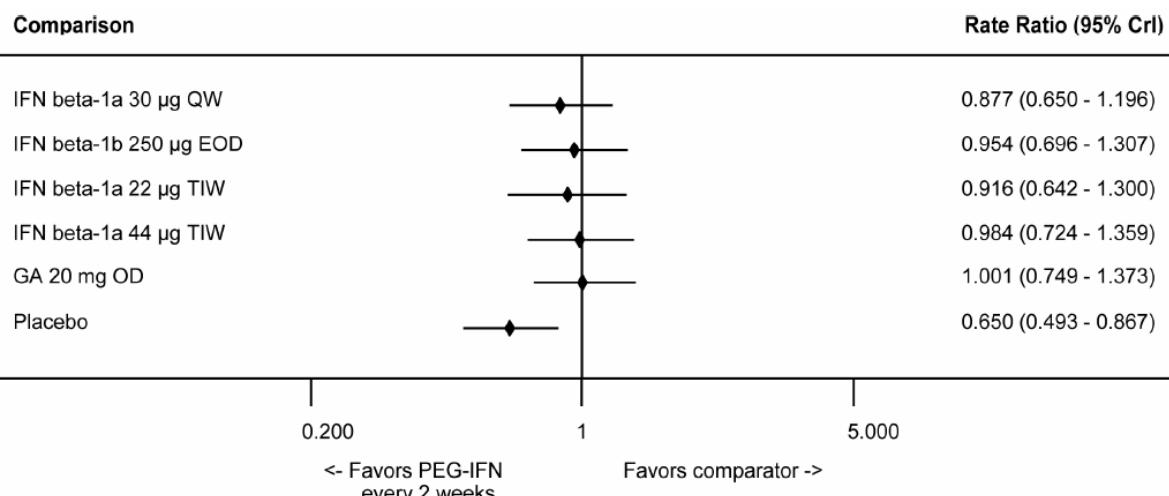


Fig 5. Summary Plot Showing Relative ARR of Peginterferon Beta-1a vs Other Injectables (RR and 95% CrI). Effect size <1 indicates favorable efficacy of intervention. Abbreviations: ARR, annualized relapse rate; CrI, credible interval; EOD, every other day; GA, glatiramer acetate; IFN, interferon; OD, once daily; PEG, pegylated; QW, once a week; RR, rate ratio; TIW, 3 times a week.

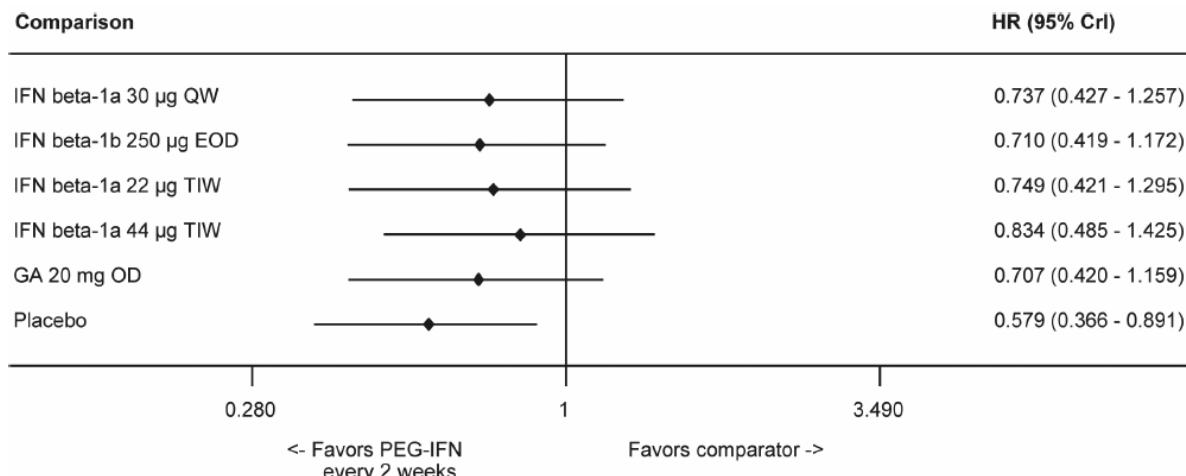
- Indirekter Vergleich Ranking:

**Table 2. Rank Probability of Best Outcomes by Treatment for ARR.**

	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6	Rank 7	SUCRA
Placebo	0.00	0.00	0.00	0.00	0.01	0.56	99.43	0.00
IFN beta-1a 30 µg QW	0.34	1.60	4.56	13.91	30.76	48.81	0.02	0.30
IFN beta-1b 250 µg EOD	6.58	15.21	23.32	26.67	20.16	8.05	0.01	0.56
IFN b-1a 22 µg TIW	6.75	9.05	12.76	18.69	27.95	24.57	0.23	0.46
IFN beta-1a 44 µg TIW	17.99	27.00	25.65	20.84	7.58	0.94	0.00	0.71
GA 20 mg OD	26.09	36.28	24.65	9.90	2.44	0.64	0.00	0.79
PEG IFN beta-1a 125 µg every 2 weeks	42.25	10.86	9.06	10.00	11.09	16.43	0.31	0.69

Abbreviations: ARR, annualized relapse rate; CDP3M, 3-month confirmed disability progression; CDP6M, 6-month confirmed disability progression; EOD, every other day; GA, glatiramer acetate; IFN, interferon; µg, microgram; OD, once daily; PEG, pegylated; QW, once a week; SUCRA, surface under the cumulative ranking curve; TIW, 3 times a week

- CDP3M



**Fig 6. Summary Plot Showing the CDP3M for Peginterferon Beta-1a vs Comparators (HR and 95% CrI).** Effect size <1 indicates favorable efficacy of intervention. Abbreviations: CDP3M, 3-month confirmed disability progression; CrI, credible interval; EOD, every other day; GA, glatiramer acetate; HR, hazard ratio; IFN, interferon; OD, once daily; PEG, pegylated; QW, once a week; TIW, 3 times a week.

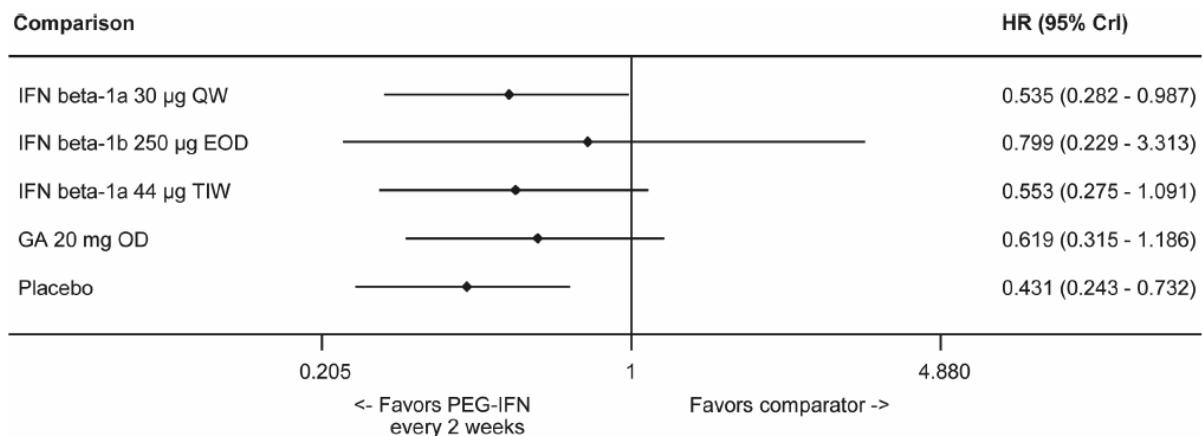
#### o Indirekter Vergleich Ranking:

**Table 3. Rank Probability of Best Outcomes by Treatment for CDP3M.**

	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6	Rank 7	SUCRA
Placebo	0.00	0.01	0.09	0.49	3.97	17.79	77.64	0.05
IFN beta-1a 30 µg QW	4.14	13.77	20.90	21.72	16.64	17.57	5.27	0.49
IFN beta-1b 250 µg EOD	2.32	9.93	14.24	20.77	26.52	20.62	5.61	0.43
IFN beta-1a 22 µg TIW	6.75	17.64	19.93	19.14	13.97	16.73	5.85	0.52
IFN beta-1a 44 µg TIW	17.94	36.73	21.62	12.14	7.92	3.25	0.41	0.72
GA 20 mg OD	1.68	8.39	14.83	20.71	28.03	21.60	4.76	0.42
PEG IFN beta-1a 125 µg every 2 weeks	67.17	13.54	8.39	5.04	2.95	2.44	0.46	0.88

Abbreviations: ARR, annualized relapse rate; CDP3M, 3-month confirmed disability progression; CDP6M, 6-month confirmed disability progression; EOD, every other day; GA, glatiramer acetate; IFN, interferon; µg, microgram; OD, once daily; PEG, pegylated; QW, once a week; SUCRA, surface under the cumulative ranking curve; TIW, 3 times a week

- CDP6M



**Fig 7. Summary Plot Showing the CDP6M for Peginterferon Beta-1a vs Comparators (HR and 95% CrI).** Effect size <1 indicates favorable efficacy of intervention. Abbreviations: CDP6M, 6-month confirmed disability progression; CrI, credible interval; EOD, every other day; GA, glatiramer acetate; HR, hazard ratio; IFN, interferon; OD, once daily; PEG, pegylated; QW, once a week; TIW, 3 times a week.

- Indirekter Vergleich Ranking:

**Table 4. Rank Probability of Best Outcomes by Treatment for CDP6M.**

	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6	SUCRA
Placebo	0.00	0.10	0.87	4.43	21.07	73.54	0.1
IFN beta-1a 30 µg QW	0.50	8.13	20.23	30.53	36.27	4.35	0.4
IFN beta-1b 250 µg EOD	37.76	25.56	8.08	6.89	8.46	13.26	0.7
IFN beta-1a 44 µg TIW	1.50	10.27	23.15	33.28	23.85	7.96	0.4
GA 20 mg OD	2.45	22.15	42.74	22.55	9.24	0.87	0.6
PEG IFN beta-1a 125 µg every 2 weeks	57.80	33.79	4.93	2.33	1.11	0.04	0.9

Abbreviations: ARR, annualized relapse rate; CDP3M, 3-month confirmed disability progression; CDP6M, 6-month confirmed disability progression; EOD, every other day; GA, glatiramer acetate; IFN, interferon; µg, microgram; OD, once daily; PEG, pegylated; QW, once a week; SUCRA, surface under the cumulative ranking curve; TIW, 3 times a week

- Adverse events:

- Comparison of AEs was not possible within the NMA. However, based on a non-meta-analyzed comparison the safety and tolerability profile of peginterferon beta-1a 125 µg every 2 weeks appears consistent with that of other evaluated treatments, with no evidence for additional AE burden.
- The most frequently reported AE for peginterferon Beta-1a, is similar between peginterferon beta-1a and IFN beta-1a 44 µg TIW, and higher than those reported for other IFNs and GA. However, similar to IFNs and GA, the majority of patient-reported injection site reactions with peginterferon beta-1a were mild or moderate, with only 3% of patients reporting severe injection-site reactions over 2 years of treatment.

### Anmerkung/Fazit der Autoren

Based on the evidence from the systematic literature review and NMA, peginterferon beta-1a demonstrated comparable efficacy compared to non-pegylated IFNs and GA in the treatment of RRMS. In addition, based on the descriptive analysis of relative safety data, peginterferon beta-1a is well-tolerated and has the potential to reduce the frequency of some of the more prevalent AEs associated with most injectable DMTs, such as flu-like symptoms and injection site reactions. The efficacy profile, the lower injection frequency, and a consistently more favorable safety profile of the peginterferon beta-1a 125 µg every 2 weeks regimen make it a suitable alternative to other approved injectable DMTs for the treatment of patients with RRMS

### Kommentare zum Review

- Heterogenität der Studien bezüglich Definition „relapse of disease“ sowie der Krankheitsdauer.

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### Mendelez-Torres G et al., 2018 [19].

Comparative effectiveness of betainterferons and glatiramer acetate for relapsing-remitting multiple sclerosis: systematic review and network meta-analysis of trials including recommended dosages

#### Fragestellung

We systematically reviewed the comparative effectiveness of injectable beta-interferons (IFN- $\beta$ ) and glatiramer acetate (GA) on annualised relapse rate (ARR), progression and discontinuation due to adverse events (AEs) in RRMS, using evidence from within the drugs' recommended dosages.

#### Methodik

##### Population:

- people diagnosed with RRMS

##### Intervention:

- injectable beta-interferons (IFN- $\beta$ ) and glatiramer acetate (GA)

##### Komparator:

- placebo or best supportive care without DMTs, or another of the interventions when used within indication

##### Endpunkte:

- relapse frequency, disease progression, and discontinuation due to adverse events, relapse rate, time to progression, or discontinuation due to adverse events

##### Recherche/Suchzeitraum:

- in January and February 2016. These update searches were limited by date to the beginning of 2012

##### Qualitätsbewertung der Studien:

- Cochrane risk of bias assessment tool

#### Ergebnisse

##### Anzahl eingeschlossener Studien:

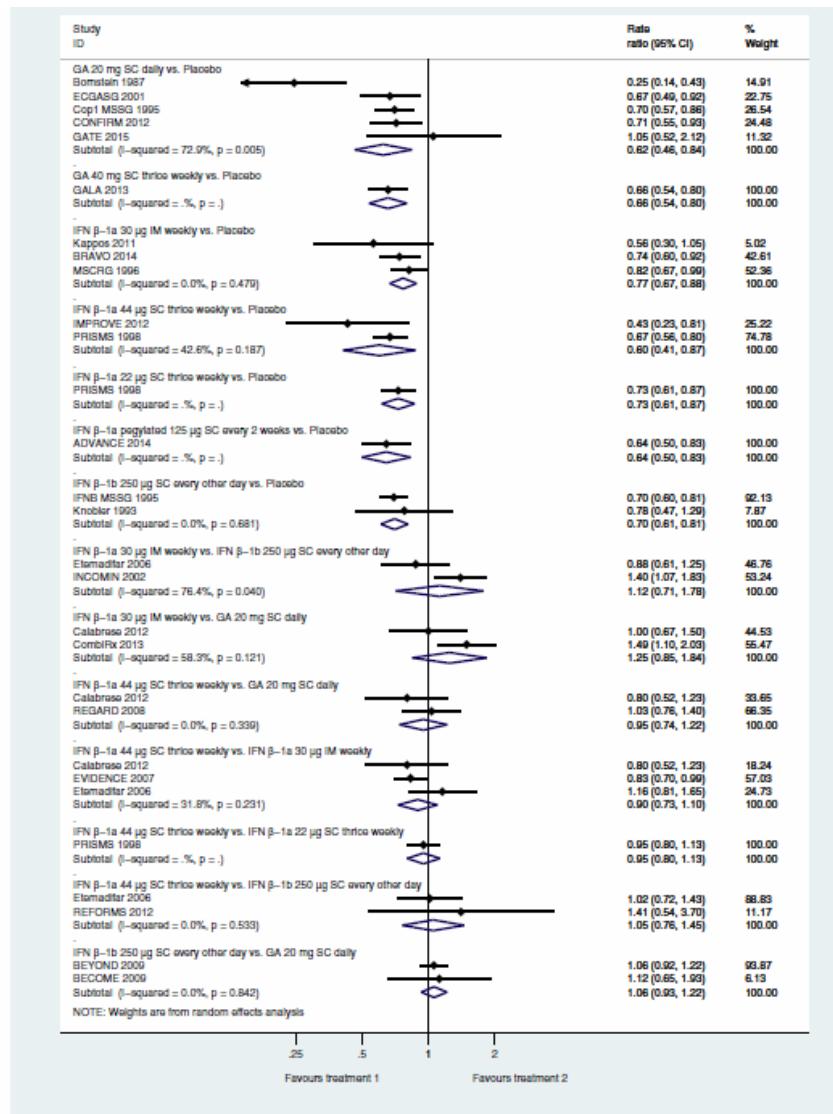
- 24 primary studies
- 14 trials were placebo-controlled, the remaining 10 trials only compared active drugs against each other. One trial reported only adverse events data. The modal follow-up was 24 months.

### Qualität der Studien:

- All studies that adequately detailed their method of randomization ( $n = 15$ , 63%) were appraised as being at low risk of bias in this domain. A similar number of studies ( $n = 15$ ) were judged to be at low risk of bias from allocation concealment, though one study was classed as at high risk of bias in this domain. We judged that most studies were at high risk of bias in blinding of participants and personnel ( $n = 24$ , 83%) and blinding of outcome assessment ( $n = 18$ , 75%) due to a combination of injection site reactions in placebo-controlled trials and an open label design. Five studies (21%) were at high risk of bias from incomplete outcome data due to differential attrition between arms, and we believed that four studies (17%) were at high risk of bias from selective reporting. Finally, most studies ( $n = 17$ , 71%) were at high risk of bias from other sources, generally stemming from industry sponsorship

### Studienergebnisse:

- All drugs had a beneficial effect on ARR as compared to placebo, but not compared to each other, and findings were robust to sensitivity analysis.



**Fig. 2** Pairwise meta-analyses for annualised relapse rate. IFN: interferon, GA: glatiramer acetate, IM: intramuscular, SC: subcutaneous

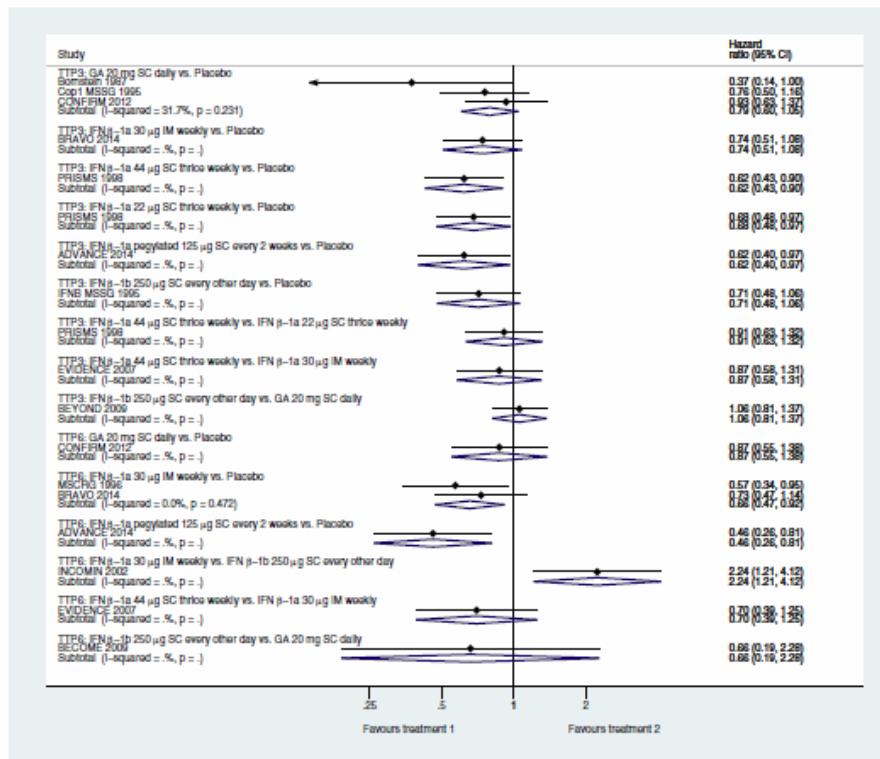
**Table 3** Network meta-analysis results for annualised relapse rate<sup>a</sup>

Drug	SUCRA	GA 20 mg daily	PegIFN β-1a 125 µg every 2 weeks	GA 40 mg thrice weekly	IFN β-1a 44 µg SC thrice weekly	IFN β-1b 250 µg SC every other day	IFN β-1a 22 µg SC thrice weekly	IFN β-1a 30 µg IM weekly	Placebo
GA 20 mg daily	0.77		1.01 (0.77, 1.33)	1.00 (0.80, 1.24)	0.97 (0.85, 1.10)	0.95 (0.86, 1.05)	0.91 (0.76, 1.08)	0.82 (0.73, 0.92)	0.65 (0.59, 0.72)
PegIFN β-1a 125 µg every 2 weeks	0.73			0.98 (0.71, 1.35)	0.95 (0.72, 1.26)	0.94 (0.71, 1.23)	0.89 (0.66, 1.21)	0.81 (0.62, 1.06)	0.64 (0.50, 0.83)
GA 40 mg thrice weekly	0.70				0.97 (0.77, 1.22)	0.96 (0.77, 1.19)	0.91 (0.71, 1.17)	0.82 (0.66, 1.03)	0.66 (0.54, 0.80)
IFN β-1a 44 µg SC thrice weekly	0.64					0.99 (0.86, 1.13)	0.94 (0.80, 1.10)	0.85 (0.76, 0.95)	0.68 (0.60, 0.76)
IFN β-1b 250 µg SC every other day	0.56						0.95 (0.79, 1.14)	0.86 (0.76, 0.97)	0.69 (0.62, 0.76)
IFN β-1a 22 µg SC thrice weekly	0.43							0.91 (0.76, 1.08)	0.72 (0.61, 0.85)
IFN β-1a 30 µg IM weekly	0.18								0.80 (0.72, 0.88)
Placebo	0								
Test for inconsistency ( $\chi^2$ , df, p)		11.71, 11, 0.38							

<sup>a</sup>Findings are expressed as rate ratio (RR) with 95% CI

IFN: interferon, GA: glatiramer acetate, IM: intramuscular, SC: subcutaneous, SUCRA: surface under the cumulative ranking curve

- We considered time to progression confirmed at 3 months and confirmed at 6 months in separate models; while both models suggested that the included drugs were effective, findings were not consistent between models.


**Fig. 3** Pairwise meta-analyses for time to progression. IFN: interferon, GA: glatiramer acetate, IM: intramuscular, SC: subcutaneous; TTP3: time to progression confirmed at 3 months; TTP6: time to progression confirmed at 6 months

**Table 4** Network meta-analysis results for time to progression<sup>a</sup>

Time to progression confirmed at 3 months

Drug	SUCRA	IFN β-1a 44 µg SC thrice weekly	PegIFN β-1a 125 µg every 2 weeks	IFN β-1a 22 µg SC thrice weekly	IFN β-1a 30 µg IM weekly	GA 20 mg daily	IFN β-1b 250 µg SC every other day	Placebo	GA 40 mg SC thrice weekly
IFN β-1a 44 µg SC thrice weekly	0.77		1.01 (0.59, 1.74)	0.92 (0.65, 1.30)	0.86 (0.62, 1.19)	0.82	0.81 (0.53, 1.22)	0.63 (0.46, 0.86)	Not included in this analysis
PegIFN β-1a 125 µg every 2 weeks	0.75			0.91 (0.52, 1.59)	0.85 (0.49, 1.46)	0.81 (0.49, 1.34)	0.80 (0.47, 1.34)	0.62 (0.40, 0.97)	
IFN β-1a 22 µg SC thrice weekly	0.62				0.94 (0.62, 1.42)	0.90 (0.59, 1.36)	0.88 (0.57, 1.36)	0.68 (0.49, 0.96)	
IFN β-1a 30 µg IM weekly	0.5					0.96 (0.65, 1.42)	0.94 (0.62, 1.43)	0.73 (0.53, 1.00)*	
GA 20 mg daily	0.44						0.98 (0.78, 1.24)	0.76 (0.60, 0.97)	
IFN β-1b 250 µg SC every other day	0.39							0.78 (0.59, 1.02)	
Placebo	0.02								
Test for inconsistency ( $\chi^2$ , df, p)	0.35, 2, 0.84								
Time to progression confirmed at 6 months									
Drug	SUCRA	IFN β-1b 250 µg SC every other day	PegIFN β-1a 125 µg every 2 weeks	IFN β-1a 44 µg SC thrice weekly	IFN β-1a 30 µg IM weekly	GA 20 mg daily	Placebo	PegIFN β-1a 125 µg every 2 weeks	GA 40 mg thrice weekly
IFN β-1b 250 µg SC every other day	0.9		0.74 (0.32, 1.71)	0.71 (0.32, 1.60)	0.50 (0.29, 0.87)	0.42	0.34 (0.18, 0.63)	Not included in this analysis	
PegIFN β-1a 125 µg every 2 weeks	0.71			0.97 (0.40, 2.33)	0.68 (0.35, 1.31)	0.56 (0.28, 1.15)	0.46 (0.26, 0.81)		
IFN β-1a 44 µg SC thrice weekly	0.7				0.70 (0.39, 1.25)	0.58 (0.27, 1.27)	0.47 (0.24, 0.98)		
IFN β-1a 30 µg IM weekly	0.4					0.83 (0.49, 1.41)	0.68 (0.49, 0.94)		
GA 20 mg daily	0.25						0.82 (0.53, 1.26)		
Placebo	0.05								
Test for inconsistency ( $\chi^2$ , df, p)	0.77, 1, 0.38								

\*Findings are presented as HR (95% CI)

IFN interferon, GA glatiramer acetate, IM intramuscular, SC subcutaneous, SUCRA surface under the cumulative ranking curve

- Discontinuation due to AEs did not appear to be different between drugs.

### Anmerkung/Fazit der Autoren

Our meta-analyses confirmed that IFN-β and GA reduce ARR and generally delay progression as defined in these trials. We found, however, that there was no clear ‘winner’ across outcomes, and our findings were qualified by the high risk of bias across studies, and the use of an impairment/mobility scale to measure disease progression. Future research should consider more relevant measures of disability and, given that most trials have been short-term, consider a longitudinal approach to comparative effectiveness.

## 3.4 Leitlinien

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**Montalban X et al., 2018 [20].**

*European Committee of Treatment and Research in Multiple Sclerosis (ECTRIMS) and the European Academy of Neurology (EAN)*

ECTRIMS/EAN Guideline on the pharmacological treatment of people with multiple sclerosis.

### **Leitlinienorganisation/Fragestellung**

To develop an evidence-based clinical practice guideline for the pharmacological treatment of people with MS.

### **Methodik**

#### Grundlage der Leitlinie

- Repräsentativität des Gremiums unklar. Keine Angaben gefunden. Unklar ob LL mit Patientenbeteiligung erstellt wurde.
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt.
- Systematische Suche, Auswahl und Bewertung der Evidenz.
- Konsensusprozesse dargelegt. Kein externes Begutachtungsverfahren dargelegt.
- Die zugrundeliegende Evidenz der Empfehlungen ist im Hintergrundtext dargestellt.
- Update soll 2020 durchgeführt werden.

#### Recherche/Suchzeitraum:

- Central, Embase, Medline, PreMedline, PsycINFO inception to December 2015

#### GoR, LoE

- The quality of evidence was rated into four categories according to the risk of bias. The recommendations with assigned strength (strong and weak) were formulated based on the quality of evidence and the risk-benefit balance.

### **Recommendations**

Review question 2: In patients with RRMS and secondary-progressive MS, what is the benefit of treating with a DMD compared to no treatment/another DMD?

Review question 3: In patients with primary-progressive MS, what is the benefit of treating with a DMD compared to no treatment?

- Offer early treatment with DMDs to patients with active RRMS as defined by clinical relapses and/or MRI activity (active lesions—contrast-enhancing lesions; new or unequivocally enlarging T2 lesions assessed at least annually). Also includes CIS fulfilling current diagnostic criteria for MS. (strong)
- For active RRMS, choosing between the wide range of available drugs (interferon beta-1b, interferon beta-1a -sc, im-, peginterferon beta-1a, glatiramer acetate, teriflunomide, dimethyl fumarate, cladribine, fingolimod, daclizumab, natalizumab, ocrelizumab and alemtuzumab) from the modestly effective to the highly efficacious, will depend on the following factors, in discussion with the patient:

- Patient characteristics and comorbidities;
  - Disease severity/activity;
  - Drug safety profile;
  - Accessibility of the drug.
- (consensus statement)
- Consider treatment with interferon-1a (sc) or -1b for patients with active secondary-progressive MS taking into account, in discussion with the patient, the dubious efficacy, as well as the safety and tolerability profile of these drugs. (weak)
  - Consider treatment with mitoxantrone for patients with active secondary-progressive MS taking into account, in discussion with the patient, the efficacy, and specifically the safety and tolerability profile of this agent. (weak)
  - Consider treatment with ocrelizumab or cladribine for patients with active secondary-progressive MS. (weak)
  - Consider treatment with ocrelizumab for patients with primary-progressive MS. (weak)

Review question 6: Treatment strategy if inadequate treatment response: In patients with relapsing MS treated with interferon or glatiramer acetate and evidence of early disease activity (relapses and/or disability progression and/or MRI activity at 6/12 months), what is the benefit of switching between interferon and glatiramer acetate versus moving to more efficacious drugs?

- Offer a more efficacious drug to patients treated with interferon or glatiramer acetate who show evidence of disease activity assessed as recommended in questions 4 and 5 (patients with relapsing MS treated with DMDs) of this guideline. (strong)
  - When deciding on which drug to switch to, in consultation with the patient, consider the following factors:
    - Patient characteristics and comorbidities;
    - Drug safety profile;
    - Disease severity/activity.
- (consensus statement)

(...)

- When treatment with a highly efficacious drug is stopped, either due to inefficacy or safety concerns, consider starting another highly efficacious drug. When starting the new drug, take into account the following factors:
  - disease activity (clinical and MRI), the greater the activity, the higher the urgency to start new treatment;
  - half life and biological activity of the previous drug;
  - the potential for resumed disease activity or even rebound (particularly with natalizumab).
  - (consensus statement)
- In treatment decisions, consider the possibility of resumed disease activity or even rebound when stopping treatment, particularly with natalizumab. (weak)

### Long-term Treatment

- Consider continuing a DMD if a patient is stable (clinically and on MRI) and shows no safety or tolerability issues. (weak)

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**Rae-Grant A et al., 2018 [21,22].**

*American Academy of Neurology (AAN)*

Practice guideline: Disease-modifying therapies for adults with multiple sclerosis

### **Leitlinienorganisation/Fragestellung**

To develop recommendations for disease-modifying therapy (DMT) for multiple sclerosis (MS).

### **Methodik**

#### Grundlage der Leitlinie

- Repräsentatives Gremium. Patientenbeteiligung.
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt.
- Systematische Suche, Auswahl und Bewertung der Evidenz.
- Konsensusprozesse und externes Begutachtungsverfahren dargelegt.
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

#### Recherche/Suchzeitraum:

- literature search of MEDLINE, CENTRAL, and EMBASE published from database inception to November 2016

#### GoR

- Level A: Must
- Level B: Should
- Level C: May
- Level U: No recommendation supported

## LoE

### *Therapeutic scheme*

#### *Class I*

A randomized controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent between treatment groups, or there is appropriate statistical adjustment for differences.

The following are also required:

- a. concealed allocation
- b. no more than 2 primary outcomes specified
- c. exclusion/inclusion criteria clearly defined
- d. adequate accounting for dropouts (with at least 80% of enrolled subjects completing the study) and crossovers with numbers sufficiently low to have minimal potential for bias.
- e. For noninferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required\*:
  - i. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or noninferiority.
  - ii. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose, and dosage adjustments are similar to those previously shown to be effective).
  - iii. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment.
  - iv. The interpretation of the study results is based upon a per-protocol analysis that accounts for dropouts or crossovers.
- f. For crossover trials, both period and carryover effects examined and statistical adjustments performed, if appropriate

#### *Class II*

An RCT of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criteria a–e above (see Class I) or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b–e above (see Class I). (Alternatively, a randomized crossover trial missing 1 of the following 2 characteristics: period and carryover effects described or baseline characteristics of treatment order groups presented.) All relevant baseline characteristics are presented and substantially equivalent among treatment groups, or there is appropriate statistical adjustment for differences.

#### *Class III*

All other controlled trials (including studies with external controls such as well-defined natural history controls). (Alternatively, a crossover trial missing both of the following 2 criteria: period and carryover effects described or baseline characteristics of treatment order groups presented.) A description of major confounding differences between treatment groups that could affect outcome.<sup>\*\*</sup> Outcome assessment is masked, objective, or performed by someone who is not a member of the treatment team.

#### *Class IV*

Studies that (1) did not include patients with the disease, (2) did not include patients receiving different interventions, (3) had undefined or unaccepted interventions or outcomes measures, or (4) had no measures of effectiveness or statistical precision presented or calculable.

\*Note that numbers 1–3 in Class Ie are required for Class II in equivalence trials. If any 1 of the 3 is missing, the class is automatically downgraded to Class III.

\*\*Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

#### Rules for determining confidence in evidence

- Modal modifiers used to indicate the final confidence in evidence in the conclusions
  - High confidence: highly likely or highly probable
  - Moderate confidence: likely or probable
  - Low confidence: possibly
  - Very low confidence: insufficient evidence
- Initial rating of confidence in the evidence for each intervention outcome pair
  - High: requires 2 or more Class I studies
  - Moderate: requires 1 Class I study or 2 or more Class II studies
  - Low: requires 1 Class II study or 2 or more Class III studies
  - Very low: requires only 1 Class III study or 1 or more Class IV studies
- Factors that could result in downgrading confidence by 1 or more levels
  - Consistency
  - Precision
  - Directness
  - Publication bias
  - Biological plausibility
- Factors that could result in downgrading confidence by 1 or more levels or upgrading confidence by 1 level

- Magnitude of effect
- Dose response relationship
- Direction of bias

## Recommendations

### Starting therapy

- Clinicians should offer DMTs to people with relapsing forms of MS with recent clinical relapses or MRI activity (Level B).
- Because of the high frequency of severe AEs, clinicians should not prescribe mitoxantrone to people with MS unless the potential therapeutic benefits greatly outweigh the risks (Level B).<sup>\*</sup> \*Level A recommendations cannot be based on related evidence alone. Recommendation downgraded to Level B.
- Clinicians should prescribe alemtuzumab, fingolimod, or natalizumab for people with MS with highly active MS (Level B).
- Clinicians may recommend azathioprine or cladribine for people with relapsing forms of MS who do not have access to approved DMTs (Level C).
- Clinicians should offer ocrelizumab to people with PPMS who are likely to benefit from this therapy unless there are risks of treatment that outweigh the benefits (Level B).

### Switching DMT

- Clinicians should discuss switching from one DMT to another in people with MS who have been using a DMT long enough for the treatment to take full effect and are adherent to their therapy when they experience 1 or more relapses, 2 or more unequivocally new MRI-detected lesions, or increased disability on examination, over a 1-year period of using a DMT (Level B).
- Clinicians should evaluate the degree of disease activity, adherence, AE profiles, and mechanism of action of DMTs when switching DMTs in people with MS with breakthrough disease activity during DMT use (Level B).
- Clinicians should discuss a change to noninjectable or less frequently injectable DMTs in people with MS who report intolerable discomfort with the injections or in those who report injection fatigue on injectable DMTs (Level B).
- Clinicians should inquire about medication AEs with people with MS who are taking a DMT and attempt to manage these AEs, as appropriate (Level B).
- Clinicians should discuss a medication switch with people with MS for whom these AEs negatively influence adherence (Level B).
- Clinicians should discuss switching DMT or reducing dosage or frequency (where there are data on different doses [e.g., interferons, teriflunomide, azathioprine]) when there are persistent laboratory abnormalities (Level B).
- Clinicians should counsel people with MS considering natalizumab, fingolimod, rituximab, ocrelizumab, and dimethyl fumarate about the PML risk associated with these agents (Level B).
- Clinicians should discuss switching to a DMT with a lower PML risk with people with MS taking natalizumab who are or become JCV antibody-positive, especially with an index of above 0.9 while on therapy (Level B).

- Clinicians should counsel that new DMTs without long-term safety data have an undefined risk of malignancy and infection for people with MS starting or using new DMTs (Level B).
- If a patient with MS develops a malignancy while using a DMT, clinicians should promptly discuss switching to an alternate DMT, especially for people with MS using azathioprine, methotrexate, mycophenolate, cyclophosphamide, fingolimod, teriflunomide, alemtuzumab, or dimethyl fumarate (Level B).
- People with MS with serious infections potentially linked to their DMT should switch DMTs (does not pertain to PML management in people with MS using DMT) (Level B).
- Clinicians should check for natalizumab antibodies in people with MS who have infusion reactions before subsequent infusions, or in people with MS who experience breakthrough disease activity with natalizumab use (Level B).
- Clinicians should switch DMTs in people with MS who have persistent natalizumab antibodies (Level B).
- Physicians and people with MS choosing to switch from natalizumab to fingolimod should initiate treatment within 8–12 weeks after natalizumab discontinuation (for reasons other than pregnancy or pregnancy planning) to diminish the return of disease activity (Level B).

#### Stopping DMT

- In people with RRMS who are stable on DMT and want to discontinue therapy, clinicians should counsel people regarding the need for ongoing follow-up and periodic reevaluation of the decision to discontinue DMT (Level B).
- Clinicians should advocate that people with MS who are stable (that is, no relapses, no disability progression, stable imaging) on DMT should continue their current DMT unless the patient and physician decide a trial off therapy is warranted (Level B).
- Clinicians may advise discontinuation of DMT in people with SPMS who do not have ongoing relapses (or gadolinium enhanced lesions on MRI activity) and have not been ambulatory (EDSS 7 or greater) for at least 2 years (Level C).

#### In people with RRMS, are DMTs superior to placebo or other DMTs in preventing disease progression as measured by in-study disease progression measures?

- The following DMTs are more effective than placebo in reducing the risk of disability progression in people with RRMS (high confidence): daclizumab HYP,<sup>20</sup> dimethyl fumarate,<sup>18,21</sup> fingolimod,<sup>9,10</sup> IFN- $\beta$ -1a 30  $\mu$ g IM weekly,<sup>22,32</sup> IFN- $\beta$ -1a 44  $\mu$ g subcutaneous 3 times weekly,<sup>11</sup> mitoxantrone,<sup>23</sup> natalizumab,<sup>12</sup> pegylated IFN,<sup>24</sup> and teriflunomide.<sup>26,33</sup> See safety note on page 791.
- The following DMTs are more effective than other DMTs in reducing the risk of disability progression in people with RRMS (high confidence): alemtuzumab (vs IFN- $\beta$ -1a 44  $\mu$ g subcutaneous 3 times weekly)<sup>15,29</sup> and ocrelizumab (vs IFN- $\beta$ -1a 44  $\mu$ g subcutaneous 3 times weekly).<sup>13</sup>
- Cladribine<sup>14</sup> is probably more effective than placebo in reducing the risk of disability progression in people with RRMS (moderate confidence).
- The following DMTs are possibly no more effective than placebo in reducing the risk of disability progression in people with RRMS (low confidence): glatiramer acetate<sup>18,34,35</sup> and pulsed corticosteroids added to IFN- $\beta$ -1a IM once weekly

- Fingolimod is possibly no more effective than IFN- $\beta$ -1a IM weekly in reducing the risk of disability progression over 1 year (low confidence).16
- IFN- $\beta$ -1a is possibly no more effective than glatiramer acetate in reducing the risk of disability progression over 3 years (low confidence).

In people with RRMS who experience disease activity while on a DMT, is changing to a different DMT superior to continuing the present DMT in terms of relapse rate and MRI detected T2 or gadolinium-enhanced lesion activity?

- For individuals with RRMS who experienced a relapse on IFN- $\beta$  or glatiramer acetate, alemtuzumab is more effective than IFN- $\beta$ -1a 44  $\mu$ g subcutaneous 3 times per week in reducing the ARR, the relapse risk, disability progression, and risk of new or enlarging T2 lesions over 2 years (high confidence).15
- In individuals with RRMS who experience 1 or more relapses in the preceding 12 months on IFN- $\beta$ , adding natalizumab is more effective than adding placebo in decreasing the risk of relapse over 2 years, the ARR, the risk of disability progression over 2 years, and the risk of new or enlarging T2 lesions at 1 year (high confidence).e3
- In individuals with RRMS who experienced one or more relapses in the preceding 12 months on glatiramer acetate, there is insufficient evidence to determine the efficacy of natalizumab added to glatiramer acetate compared with placebo added to glatiramer acetate in decreasing the risk of relapse at 6 months (very low confidence).e4
- Natalizumab added to glatiramer acetate is probably more effective than placebo added to glatiramer acetate in decreasing the cumulative number of new or enlarging T2 lesions at 6 months (moderate confidence).e4
- Note that natalizumab is not presently approved/ recommended as an add-on therapy to other DMTs owing to potential safety concerns associated with combined use of this medication.

In people with progressive MS, are DMTs superior to placebo or other DMTs as measured by relapse rate or in-study disease progression?

- The following DMTs are probably more effective than placebo in reducing the risk of relapse in people with progressive MS (moderate confidence): IFN- $\beta$ -1a 60  $\mu$ g IM weekly (SPMS)e7 and mitoxantrone (worsening RRMS and SPMS).e8
- There is insufficient evidence to determine the efficacy of the following DMTs compared with placebo in reducing the risk of relapse in people with progressive MS (very low confidence): azathioprine,<sup>38</sup> immunoglobulins,e9,e10 and methotrexate (chronic progressive MS, older terminology that is undefined but included present PPMS and SPMS disease types).e11 There is insufficient evidence to determine the efficacy of high-dose corticosteroids compared with low-dose corticosteroidse12 in reducing the risk of relapse in people with SPMS (very low confidence).
- The following DMTs are probably more effective than placebo in reducing the risk of in-study disability progression in people with progressive MS (RRMS or SPMS; moderate confidence): mitoxantrone (worsening RRMS and SPMS)e13 and ocrelizumab (PPMS).e14
- The following DMTs are possibly no more effective than placebo in reducing the risk of in-study disability progression in people with progressive MS (low confidence): cladribine (SPMS),e15 fingolimod (PPMS),e16 glatiramer acetate (progressive forms of MSe17 and PPMSe18), IFN- $\beta$ -1a 30  $\mu$ g IM weekly (SPMSe7 and PPMSe19), IFN- $\beta$ -1a subcutaneous 3

times per week (SPMS),e20 IFN- $\beta$ -1b subcutaneous alternate day (SPMSe5,e6 and PPMSe21), and rituximab (PPMS).e22

- There is insufficient evidence to determine the efficacy of the following DMTs relative to placebo in reducing the risk of instudy disability progression in people with progressive MS (very low confidence): azathioprine,<sup>38</sup> corticosteroids added to mitoxantrone,<sup>e23</sup> cyclophosphamide,<sup>e24,e25</sup> immunoglobulins, e9,e10 and methotrexate (CPMS [PPMS]).e11

## 4 Detaillierte Darstellung der Recherchestrategie

**Cochrane Library - Cochrane Database of Systematic Reviews (Issue 1 of 12, January 2020) am 03.02.2020**

#	Suchfrage
1	[mh "multiple sclerosis"]
2	(multiple NEXT scleros*):ti,ab,kw
3	#1 OR #2
4	#3 with Cochrane Library publication date from Feb 2015 to Feb 2020

**Systematic Reviews in Medline (PubMed) am 03.02.2020**

#	Suchfrage
1	multiple sclerosis/therapy[mh]
2	multiple scleros*[ti]
3	((ms[ti]) OR rms[ti]) OR rrms[ti]) OR spms[ti]
4	multiple scleros*[tiab]
5	(#2) OR (#3 AND #4)
6	(#5) AND ((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]))
7	(#1) OR (#6)
8	(#7) 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 study[pt] OR validation study[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

#	Suchfrage
	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[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])))))
9	(#8) AND ("2015/02/01"[PDAT] : "3000"[PDAT])
10	(#9) NOT "The Cochrane database of systematic reviews"[Journal]
11	(#10) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
12	(#11) NOT (retracted publication [pt] OR retraction of publication [pt])

#### Leitlinien in Medline (PubMed) am 03.02.2020

#	Suchfrage
1	multiple sclerosis[mh]
2	multiple scleros*[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 ("2015/02/01"[PDAT] : "3000"[PDAT])
6	(#5) NOT (retracted publication [pt] OR retraction of publication [pt])

## Referenzen

1. **Berardi A, Siddiqui MK, Treharne C, Harty G, Wong SL.** Estimating the comparative efficacy of cladribine tablets versus alternative disease modifying treatments in active relapsing-remitting multiple sclerosis: adjusting for patient characteristics using meta-regression and matching-adjusted indirect treatment comparison approaches. *Curr Med Res Opin* 2019;35(8):1371-1378.
2. **Fogarty E, Schmitz S, Tubridy N, Walsh C, Barry M.** Comparative efficacy of disease-modifying therapies for patients with relapsing remitting multiple sclerosis: Systematic review and network meta-analysis. *Mult Scler Relat Disord* 2016;9:23-30.
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