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Review

Timing of high-efficacy therapy in relapsing-remitting multiple sclerosis: A systematic review

Bernd Merkel [a,b], Helmut Butzkueven [a,b], Anthony L. Traboulsee [c], Eva Havrdova [d], Tomas Kalincik [a,b,*]

[a] Department of Medicine, University of Melbourne, 300 Grattan St, Melbourne 3050, Australia
[b] Department of Neurology, Royal Melbourne Hospital, 300 Grattan St, Melbourne 3050, Australia
[c] Department of Medicine, University of British Columbia, 2211 Wesbrook Mall, Room s199, Vancouver V6T 2B5, Canada
[d] Department of Neurology, Center of Clinical Neuroscience, First Faculty of Medicine, General University Hospital, Charles University in Prague, Karlovo namesti 22, Prague 12800, Czech Republic

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ABSTRACT

Background: Immunotherapy initiated early after first presentation of relapsing-remitting multiple sclerosis is associated with improved long-term outcomes. One can therefore speculate that early initiation of highly effective immunotherapies, with an average efficacy that is superior to the typical first-line therapies, could further improve relapse and disability outcomes. However, the most common treatment strategy is to commence first-line therapies, followed by treatment escalation in patients who continue to experience on-treatment disease activity. While this monitoring approach is logical, the current lack of effective regenerative or remyelinating therapies behoves us to consider high-efficacy treatment strategies from disease onset (including induction therapy) in order to prevent irreversible disability.

Objective: In this systematic review, we evaluate the effect of high-efficacy immunotherapies at different stages of MS.

Methods: A systematic review of literature reporting outcomes of treatment with fingolimod, natalizumab or alemtuzumab at different stages of MS was carried out.

Results and conclusions: Twelve publications reporting relevant information were included in the systematic review. The literature suggests that treatment with high-efficacy immunotherapies is more potent in suppressing relapse activity when initiated early vs. with a delay after the MS diagnosis. The evidence reported for disability and MRI outcomes is inconclusive.

Contents

Abbreviations: DMT, disease modifying therapy; EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; MS, multiple sclerosis.

* Corresponding author at: L4 Centre, Melbourne Brain Centre, Royal Melbourne Hospital, 300 Grattan St, Parkville, VIC 3050, Australia.
E-mail address: tomas.kalincik@unimelb.edu.au (T. Kalincik).

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1. Introduction

A variety of pharmacological therapies for Multiple Sclerosis (MS) have become available during the last decade [1]. In particular, several "high-efficacy", i.e. more potent but riskier, disease-modifying therapies (DMTs), such as fingolimod, natalizumab and alemtuzumab, are now widely available to treat relapsing-remitting MS (RRMS).

Effective prevention of MS relapses partially ameliorates accumulation of long-term neurological disability [2,3]. A number of studies indicated that early initiation of DMTs leads to improved disease control and long-term outcomes when compared to delayed commencement of MS therapy [4–10]. Moreover, active MS management with high-efficacy DMTs reduces relapse activity, disability accrual and irreversible brain atrophy to a greater extent than lower-efficacy treatments, such as interferon-β or glatiramer acetate [11–14]. However, the high-efficacy DMTs are also associated with a higher risk of serious adverse events. Therefore, the most common strategy of MS management globally is "escalation therapy": patients commence treatment with lower-risk lower-efficacy DMTs and only those with demonstrated break-through disease activity escalate therapy to high-efficacy DMTs. To a significant extent, this is also the strategy mandated by payers and regulators in European countries, Canadian provinces and in the U.S.

However, the hypothesis that early treatment with high-efficacy DMTs (also comprising "induction therapy" in which DMTs with prolonged effects, such as alemtuzumab or mitoxantrone, are used first-line) could result in better disease control and improved long-term disease outcomes compared to the later commencement of high-efficacy DMTs in escalation therapy is cogent and worthy of examination.

In this systematic review, we summarise published evidence about the importance of the timing of high-efficacy DMTs (including the escalation and induction strategies), in particular natalizumab, fingolimod and alemtuzumab. Furthermore, different ways of assessing "early" and "delayed" treatment are examined, including disease duration, age, neurological disability and prior treatment status.

2. Methods

2.1. Search strategy and selection criteria

We conducted a systematic search in the databases Ovid Medline [1950-May 2016], EMBASE [1947-May 2016] and Cochrane Database of Systematic Reviews [1998-May 2016] to identify reports of clinical studies, clinical trials, comparative studies, multicentre studies, observational studies or randomised controlled trials. The search terms included 'fingolimod' OR 'natalizumab' OR 'alemtuzumab' and both 'Multiple Sclerosis' AND 'Relapsing-Remitting Multiple Sclerosis'. Publication types included article, journal article, review, review literature, meta-analysis, scientific integrity review and systematic review(s), limited to English language publications. Titles were screened first, and – where relevant – abstracts and full text articles were assessed. Conference abstracts were excluded.

Two reviewers independently reviewed titles, abstracts and full text manuscripts and disagreements were resolved by consensus. For each article, first author, year of publication, number of patients included, the DMT examined and study endpoints were extracted. All relevant endpoints and treatment outcomes of the studies including patients treated with high-efficacy DMTs were assessed if available: annualised relapse rate (ARR), Expanded Disability Status Scale (EDSS) score and EDSS confirmed progression or regression events, and the reported magnetic resonance imaging (MRI) metrics.

3. Results of the literature search

Of the 292 identified publications, 39 full text articles were reviewed, based on their titles and abstracts. Finally, twelve papers reporting relevant information on high-efficacy DMT exposure were identified for this review. An overview of the study selection process is summarised in the PRISMA flow chart (Fig. 1) and relevant outcomes of the included studies are shown in Table 1.

4. Defining early and delayed high-efficacy therapy

A great variability in the definition of "early" and "delayed" high-efficacy therapy is reflected by the published literature.

The most commonly used definition of *early*/*delayed* treatment is based on the time from the first clinical presentation of MS. The definition of a 'cut-off' for the early vs. delayed dichotomy is unclear and, in fact, somewhat arbitrary. While subgroup analysis of the CAMMS223 studied subgroups with <1.3 and ≥1.3-year disease duration [15], two observational studies of natalizumab used a cut-off of 6 years [16,17]. A number of trial extensions assigned patients originally randomised to placebo or comparator therapy to active therapy after they have completed randomised stages of the trials. This approach enables limited comparative evaluation of treatment effects delayed by 0.5–2 years [18–20]. One may argue that such delay is too short to tease out clinically relevant differences between earlier and delayed high-efficacy treatment. Moreover, regression to the mean can confound disease outcomes in extension trial settings [21]. Also, the extensions of active comparator trials are more relevant to the clinical dilemma of induction vs. escalation than extensions of placebo-controlled trials.

Relapse activity and the probability of disability accrual or improvement are functions of age; in particular MS activity has been shown to be more closely associated with patient age than clinical disease duration [21,22]. Several studies stratified patient cohorts into two age subgroups, usually using a cut-off of 40 years, but another study defined early treatment as DMT commenced before the age of 31 years [15,23–25].

Stratifying cohorts by disability at the start of therapy provides only loose association with age or disease duration, but it takes into consideration cumulative neurological impairment, a function of time and prior disease severity. Baseline disability was utilised in some subgroup analyses to stratify cohorts, using EDSS steps of 2 or 3.5 as cut-offs [15,24–26].

Early high-efficacy therapy can also be considered as the first-line treatment with highly active immunotherapies in treatment-naïve patients irrespective of their age or disability, although usually at short disease duration [14,25–28]. This perspective is highly clinically relevant, as it overlaps with the concept of induction therapy (which can be defined as treatment with high-efficacy DMTs with long-term sustained biological effect in treatment-naïve patients). As of today, escalation strategy is the dominant treatment paradigm used in clinical practice and therefore exposure of treatment-naïve patients to high-efficacy therapy (in jurisdictions where induction therapy is an available option) is likely to reflect their underlying aggressive disease state (thus increasing the risk of indication bias in observational studies).

5. Study outcomes of early vs. delayed treatment with high-efficacy DMTs

5.1. Fingolimod

Fingolimod is a sphingosine 1-phosphate receptor modulator and the first widely available MS-specific oral DMT. Within the fingolimod

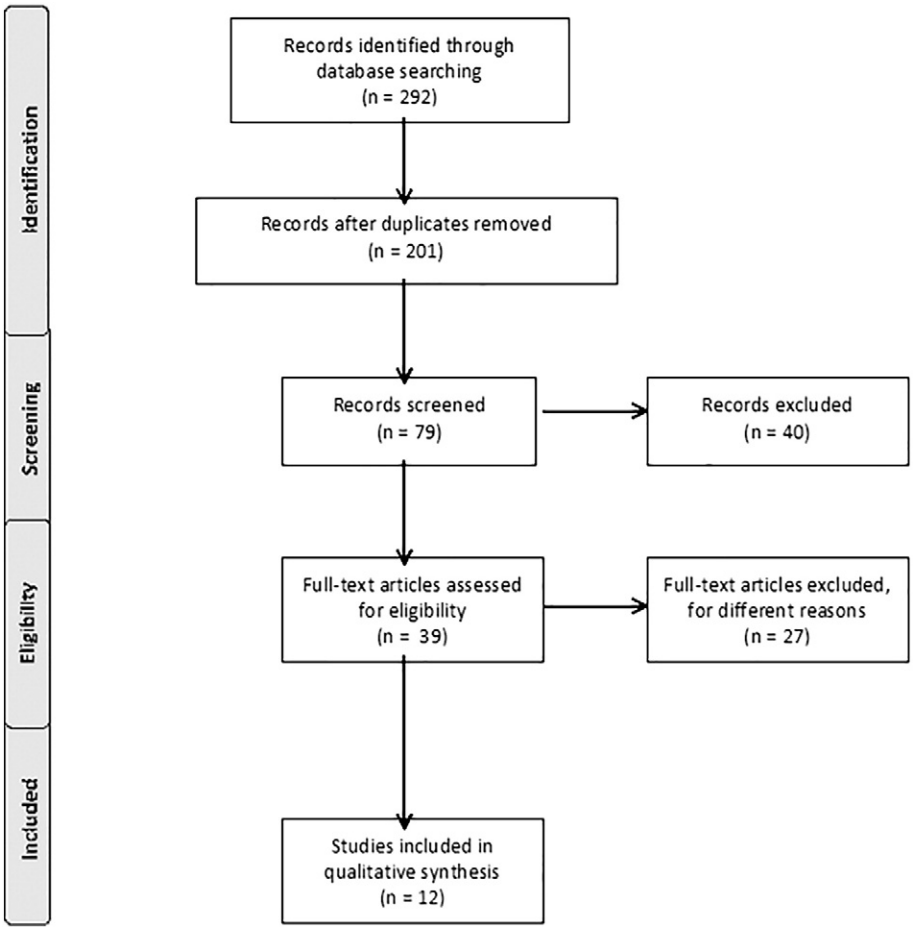

Fig. 1. PRISMA flow chart.

groups of the 12-month phase 3 TRANSFORMS trial, treatment-naïve patients had a significantly lower ARR (0.17 for the 1.25 mg group; 0.15 for the 0.5 mg group; N = 487) than those with prior exposure to DMTs (ARR = 0.33 for the 1.25 mg group; ARR = 0.26 for the 0.5 mg group; N = 559), yet no statistical comparisons between treatment-naïve and treated patients were reported [14]. A subgroup analysis of TRANSFORMS suggested a trend towards relatively higher efficacy of fingolimod (0.5 mg) among patients younger than 40 years [23]. However, no trends among patients stratified based on their pre-trial treatment status were observed.

An extension of TRANSFORMS used re-randomisation of the interferon-β arm to fingolimod 0.5 mg or 1.25 mg after 12 months, thus enabling the comparison of fingolimod administered at randomisation versus with a 12-month delay [18]. Following the switch from interferon-β to fingolimod, ARR decreased significantly. Importantly, ARR during the initial year on fingolimod was lower among the patients who were originally randomised to fingolimod (early high-efficacy therapy) in TRANSFORMS (0.12 for the 0.5 mg group and 0.15 for the 1.25 mg group) than in those re-randomised to fingolimod (delayed cohort) in the TRANSFORMS extension after one year of exposure to interferon-β (0.22 for the 0.5 mg group and 0.18 for the 1.25 mg group). Similarly, the number of new or enlarged hyperintense T2 lesions decreased and the proportion of patients free from new MRI activity increased after switching from interferon-β to fingolimod. In contrast to the relapse comparisons, the number of new or enlarged MRI lesions during the initial year on fingolimod tended to be lower in those who switched from interferon-β (0.7 for the 0.5 mg group and 1.0 for the 1.25 mg group) than those originally randomised to fingolimod (1.6 for the 0.5 mg group and 1.4 for the 1.4 mg group). There was no difference in the cumulative hazard of disability progression events between early fingolimod-exposed patients and those switched to fingolimod after one year.

The 24-month extension of FREEDOMS included 300 RRMS placebo-treated patients who were re-randomised to fingolimod at either the 0.5 mg or 1.25 mg daily dose after 24 months [19]. Switch from placebo to fingolimod resulted in a decreased ARR, in keeping with the TRANSFORMS extension. ARR during the initial year of treatment with fingolimod tended to be lower among the patients originally randomised to fingolimod 1.25 mg in FREEDOMS (0.12) than in those re-randomised to fingolimod after 24 months of assignation to placebo (0.21). However, this observation was not replicated in the fingolimod 0.5 mg groups (ARR of 0.21 and 0.19, respectively). Again, the number of new or newly enlarged T2 MRI lesions showed an inverse trend in the 0.5 mg group. During the first year of 0.5 mg fingolimod, the mean number of new or enlarged lesions tended to be lower in the group re-randomised to fingolimod after 2 years of placebo (1.43) than in the group first assigned to fingolimod (2.66). This finding was not replicated in the fingolimod 1.25 mg groups. The study did not report confirmed disability progression during the FREEDOMS extension.

A post-hoc analysis of the TRANSFORMS and FREEDOMS trials showed that the reduction in ARR was relatively more pronounced among patients who commenced fingolimod within 3 years of their first symptom [29]. A 5-year extension of a phase 2, placebo-controlled trial (N = 250) included 93 patients treated with fingolimod 0.5 mg or 5.0 mg daily after 6-month exposure to placebo [20]. In contrast to the results of the TRANFORMS and FREEDOMS trials, ARR during the initial 6 months on fingolimod tended to be higher in patients treated with fingolimod from the onset of the trial (0.36 for the 0.5 mg group and

Table 1
Summary of the studies included in the systematic review.

Study reference (name)[d]	Intervention	Subgroups	N's	Follow-up duration	ARR	EDSS progression[e]	MRI
Cohen 2010 [1] (TRANSFORMS)	Fingolimod	FTY 0.5 mg	431	12 months	[a]0.16 [0.12; 0.21]	[b] −0.08 ± 0.79	Gd + T1, T2, PBVC
		FTY 1.25 mg	426		0.20 [0.16; 0.26]	−0.11 ± 0.90	
		IFNβ	435		0.33 [0.26; 0.42]	0.01 ± 0.78	
Khatri 2011 [2] (TRANSFORMS)	Fingolimod	IFNβ to FTY 0.5 mg	167	≤24 months	[a]0.33 [0.27;0.39] (pooled)	N/A	Gd + T1, T2, PBVC
		IFNβ to FTY 1.25 mg	174				
		FTY 0.5 mg	356		0.18 [0.14;0.22]		
		FTY 1.25 mg	330		0.20 [0.16;0.25]		
Radue 2012 [3] (FREEDOMS)	Fingolimod	FTY 0.5 mg	425	24 months	N/A	N/A	Gd + T1, T2
		FTY 1.25 mg	429				
		Placebo	418				
Cohen 2013 [4] (TRANSFORMS)	Fingolimod (subgroup analysis)	FTY 0.5 mg	429	12 months	N/A	N/A	Gd + T1, T2, PBVC
		IFNβ	431				
Barkhof 2014 [5] (TRANSFORMS)	Fingolimod	FTY 0.5 mg	429	12 months	N/A	[a] −0.058 [−0.16;0.05]	Gd + T1, T2, PBVC
		FTY 1.25 mg	420			−0.021 [−0.13;0.09]	
		IFNβ	431			−0.005 [−0.11;0.10]	
Izquierdo 2014 [6]	Fingolimod	Placebo/FTY	93	≤60 months	0.23	[a,c]0.66 [0.54;0.79]	Gd + T1, T2, PBVC
		FTY 1.25 mg	94		0.17	0.71 [0.60;0.83]	
		FTY 5 mg	94		0.19	0.60 [0.47;0.72]	
Kappos 2015 [7] (FREEDOMS ext)	Fingolimod	Placebo to FTY 0.5 mg	154	[b]22.0 ± 6.8 mo	[a]0.36 [0.31;0.41] (pooled)	[a,c]0.73 [0.68;0.77] (pooled)	Gd + T1, T2, PBVC
		Placebo to FTY 1.25 mg	145	20.6 ± 8.1 mo			
		FTY 0.5 mg	330	21.8 ± 6.8 mo	0.19 [0.16;0.22]	0.80 [0.76;0.84]	
		FTY 1.25 mg	287	21.1 ± 7.4 mo	0.16 [0.14;0.20]	0.79 [0.75;0.84]	
Putzki & Maurer 2010 [8]	Natalizumab (retrospective)	NAT ≥ 12 months prior	97	[b]19.3 ± 6.1 mo	[b]0.2 ± 0.1 (12 mo)	−0.4 (12 mo)	Gd + T1, T2
Putzki & Buehler 2010 [9]	Natalizumab (retrospective)	NAT ≥ 12 months prior	85	[b]18.4 ± 2.6 mo	[b]0.3 ± 0.3 (12 mo)	−0.2 (12 mo)	Gd + T1, T2
Kallweit 2012 [10]	Natalizumab (observational)		64	≥12 months	[b]0.37 ± 0.66 (12 mo)	−0.47 (12 mo)	N/A
Butzkueven 2014 [11] (TOP)	Natalizumab	0 prior DMT	437	26 months (range: 1–69)	0.18	N/A	N/A
		1 prior DMT	2213		0.22		
		≥2 prior DMTs	2171		0.31		
Coles 2011 [12] (CAMMS223)	Alemtuzumab	Alemtuzumab 24 mg	108	36 months	[a]0.08 [0.06; 0.12]	[a] −0.45 [−0.68;-0.23]	T2, PBVC
		Alemtuzumab 12 mg	107		0.12 [0.08; 0.16]	−0.33 [−0.55;-0.10]	
		IFNβ	107		0.35 [0.29; 0.43]	0.38 [0.13; 0.63]	

Abbreviations: ARR: annualised relapse rate; EDSS: Expanded Disability Status Scale; MRI: magnetic resonance imaging; N/A: parameter was not assessed; Gd + T1: Gadolinium-enhanced T1-weighted MRI; T2: T2-weighted MRI; PBVC: partial brain volume changes; FTY: fingolimod; NAT: natalizumab; IFNβ: interferon-β; mo: months.
[a] Values given as mean [95% CI].
[b] Values given as mean ± SD.
[c] Kaplan-Meier estimates: proportion of patients free from 6-month confirmed disability progression at end of study.
[d] Studies/references are grouped by intervention first and then sorted by year of publication.
[e] Absolute score changes during follow-up duration, if not mentioned elsewhere.

0.38 for the 5.0 mg group) compared to the patients re-randomised to fingolimod after 6 months (0.21).

Several studies also evaluated changes in volumetric MRI parameters. In a post-hoc subgroup analysis of the FREEDOMS trial, fingolimod tended to reduce brain volume loss in previously treated patients (reducing brain volume change by 49% for the 0.5 mg group and 36% for the 1.25 mg group relative to placebo) more effectively than in treatment-naïve patients (reducing brain volume change by 24% for the 0.5 mg group and 29% for the 1.25 mg group relative to placebo) [27]. Interestingly, when stratified by EDSS (≤3.5 vs. >3.5), the subgroup with greater disability showed consistently greater brain volume loss, but the therapeutic effect of treatment on percentage reduction of brain volume was retained, compared to the low-disability subgroup (42% vs. 33% for fingolimod 0.5 mg and 32% vs. 33% for fingolimod 1.25 mg, high- vs. low-disability groups, respectively).

In the TRANSFORMS extension, the mean percentage change in brain volume recorded during the initial year on treatment with fingolimod tended to be greater in patients randomised to fingolimod in the original TRANSFORMS trial (−0.29% for the 0.5 mg group and −0.26% for the 1.25 mg group) than in the patients assigned to fingolimod after having initially been exposed to interferon-β (−0.22% for the 0.5 mg group and −0.14% for the 1.25 mg group) [18].

Subgroup analysis of the TRANSFORMS trial showed that the effect of fingolimod on percentage brain change was more apparent among previously treated patients than among treatment naïve-patients over a 12-month period [25]. The effect also tended to be more pronounced in the subgroup with EDSS score > 3.5 than in the subgroup with EDSS score ≤ 3.5. Finally, the degree of improvement in brain volume change appeared to be similar in patients older vs. younger than 40 years.

5.2. Natalizumab

Natalizumab is a humanized monoclonal antibody against cell adhesion molecule α4-integrin. In the subgroup analyses of the AFFIRM and SENTINEL trials, natalizumab tended to control relapses more effectively in younger patients and in patients with lower EDSS scores [24]. The ARR risk ratios for the subgroups of <40 years vs. ≥40 years were reported as 0.28 vs. 0.45 (AFFIRM) and 0.36 vs. 0.58 (SENTINEL), respectively. The ARR risk ratios for the subgroups with EDSS score ≤ 3.5 vs. EDSS > 3.5 were reported as 0.31 vs. 0.49 (AFFIRM) and 0.44 vs. 0.51 (SENTINEL), respectively. Cumulative hazard of 3-month confirmed disability progression was clearly associated with patient age and, to a much lesser extent, baseline disability. The hazard ratios for the time to first disability progression event for the subgroups of <40 years vs. ≥40 years were reported as 0.42 vs. 0.84 (AFFIRM) and 0.70 vs. 0.84 (SENTINEL), respectively. The hazard ratios for the subgroups with baseline EDSS score ≤ 3.5 vs. EDSS > 3.5 were reported as 0.55 vs. 0.69 (AFFIRM) and 0.78 vs. 0.64 (SENTINEL), respectively.

Two retrospective multicentre studies analysed data from patients who were exposed to natalizumab after failure of other DMTs [16,17]. In the first study, 85 RRMS patients were treated for a mean duration of 18.4 months [16]. Here, a trend towards a higher ARR was reported in patients with >6-year disease duration compared to those with ≤6-year disease duration. In the second study, 97 patients received natalizumab for a mean duration of 19.3 months [17]. Patients with longer disease duration (>6 years) showed significantly higher mean ARR (0.23) compared to patients with shorter (≤6 years) disease duration (0.09).

Additionally, a 5-year interim analysis of the multicentre, prospective Tysabri Observational Program (TOP) included >4800 patients treated with natalizumab and followed for a median of 3 years [26]. Patients with EDSS score < 3 experienced lower on-treatment ARR (0.27) than those with EDSS ≥ 3 (0.33). Those with no prior exposure to DMTs reported lower mean on treatment ARR (0.18) than those with one (0.22) or multiple prior DMTs (0.31).

In contrast, an observational single-centre study following 64 patients treated with natalizumab for 12 months reported a comparable ARR reduction (85%) in patients previously treated with interferon-β or glatiramer acetate and treatment-naïve patients [28]. However, the power of this study was limited by the small sample size and short follow-up duration.

5.3. Alemtuzumab

Alemtuzumab is an anti-CD52 monoclonal antibody that leads to profound pan-lymphocyte depletion. A subgroup analysis of the 3-year phase 2 CAMMS223 trial suggested a marginally greater effectiveness of alemtuzumab in reducing ARR among younger patients (hazard ratios 0.27 for <31 years vs. 0.29 for ≥31 years) and in patients with shorter disease duration (0.26 for <1.3 years vs. 0.30 for ≥1.3 years) [15]. Alemtuzumab tended to prevent disability accrual more effectively in younger patients (hazard ratios 0.18 for <31 years vs. 0.41 for ≥31 years), patients with shorter disease duration (0.23 for <1.3 years vs. 0.36 for ≥1.3 years) and lower disability (0.25 for EDSS score < 2 vs. 0.33 for EDSS ≥ 2). Similarly, its association with confirmed reduction in disability was more pronounced among younger patients (4.0 for <31 years vs. 1.5 for ≥31 years) and patients with shorter disease duration (4.0 for <1.3 years vs. 1.8 for ≥1.3 years).

6. Discussion

6.1. Critical review of the literature

Twelve publications, including nine reports of randomised clinical trials and three studies of observational data were identified as reporting information relevant to the outcomes of early vs. delayed high-efficacy DMTs for RRMS. While we have not identified any trials directly comparing the effectiveness of the two treatment paradigms, relapse, disability and MRI outcomes were reported for patients in whom treatment with fingolimod, natalizumab or alemtuzumab was delayed for up to two years. In addition, subgroup analyses of pivotal randomised clinical trials assessed effectiveness of these therapies stratified by different patient and disease characteristics, including age, disease duration or disability. A number of these studies suggested that earlier commencement of high-efficacy DMTs resulted in more effective control of relapse activity than their later initiation. One may speculate that this implies a relatively greater efficacy of high-efficacy DMTs among patients with higher inflammatory activity, e.g. such as during the earlier MS stages [21,30]. Regression to the mean may represent a confounding phenomenon, as trial baseline, by virtue of inclusion criteria, often requires the presence of a significant pre-baseline and recent relapse and/or MRI lesion activity. On the other hand, several studies did not replicate these trends (Table 2). Moreover, when MRI activity was considered in early vs. delayed high-efficacy DMTs, the reported trends were inconsistent with those reported for ARR. In addition the reported trends for the effect of early high-efficacy therapy on ARR and global brain volume were also discordant. This could potentially be attributed to a 'therapeutic lag', whereby DMTs may show more immediate effect on the inflammatory MS activity than on its consequences, such as the loss of brain tissue. Alternatively, pseudoatrophy of the brain due to treatment-induced reduction in inflammation could contribute to the greater early brain volume loss in treatment-naïve patients relative to previously treated patients [31]. In summary, the currently available evidence for early vs. delayed high-efficacy DMTs remains limited and inconclusive.

In comparison to patients with high inflammatory activity, patients with relatively low MS-related inflammation at baseline derive less benefit from treatment with high-efficacy DMTs [32]. For example, compared with injectable DMTs, natalizumab resulted in a reduction in both ARR and the risk of 3-month confirmed disability progression among patients who previously experienced on-treatment breakthrough disease activity [13], but only in a reduction in ARR when used as a first-line therapy [33]. Similarly, both CARE-MS trials demonstrated a reduction in ARR, brain volume loss and the number of new or enlarging brain lesions for alemtuzumab compared to interferon β-1a, but only CARE-MS2 showed an effect on the 6-month confirmed progression of disability and an overall improvement in disability [34,35], a conclusion that was recently replicated in an observational setting [36]. Notably, CARE-MS2 only included patients with prior relapses on injectable DMTs, whereas CARE-MS1 studied patients previously treatment-naïve. These observations suggest that the relative benefit from early high-efficacy therapy depends on the severity of the underlying disease, for example measured as prior break-through relapses on injectable DMTs. Given the relatively greater risks inherent in high-efficacy DMTs, careful selection of patients who may potentially benefit from early high-efficacy therapy is critical. Accurate predictors of individual treatment response are a key to evidence-based assessment of the risks and benefits of early high-efficacy therapy.

Recent advances in research led to novel treatment options, not included in this review as their extension studies were not published or whose widespread regulatory approvals are still pending, including ocrelizumab, ofatumuab and cladribine. Daclizumab, an anti-IL2 receptor antibody, showed improved relapse, disability and MRI outcomes [37,38]. The SELECTION trial, a 52-week extension of the SELECT trial, showed a trend towards reduced relapse activity and brain atrophy during the initial year of treatment in people who were originally randomised to daclizumab versus those with treatment delayed by 1 year [39].

There is a demand for better evidence regarding long-term outcomes of different early treatment strategies. However, duration of typical randomised clinical trials is limited to 2–3 years, with their typical 1–2 year extension studies enabling clinical and MRI follow-up up to 5-years [18–20,40]. Quality observational data and rigorous statistical methodology hold the promise of generating much-needed evidence regarding long term treatmet outcomes [41]. A comprehensive systematic review of the published observational studies showed that fingolimod markedly modified disease outcomes and was superior to injectable therapies, interferon β and glatiramer acetate [42]. Similarly, the effect of natalizumab on reducing disease activity and improving disability outcomes was found to be superior to most of the other available immunotherapies, particularly in patients with highly active disease [43–47]. Furthermore, the role of B cells in the propagation of MS, including the accrual of disability, has been established; [48] it is therefore not surprising that B-cell therapies have become an important strategy to achieve control of active disease [49]. We propose to conduct a propensity score-matched evaluation of short- and medium-term disease outcomes among patients exposed to these high-efficacy therapies in a large international observational cohort study. The questions that require further attention are those of clinical and MRI outcomes of (i) early initiation of injectable vs. high-efficacy immunotherapies, (ii)

Table 2
Summary of the relevant outcomes of the studies included in this review, with arrows indicating reported trends: ↑ the outcome measure increased after early high-efficacy treatment, - no differences between early vs. delayed high-efficacy treatment, ↓ the outcome measure decreased after early high-efficacy treatment.

Study reference (name)	Intervention	Study type	Features defining early treatment	Outcome	Trend in early (vs. delayed) high-efficacy treatment[a]
Cohen 2010 [1] (TRANSFORMS)	Fingolimod	Subgroup	No prior exposure to DMTs	ARR	↓
Cohen 2013 [2] (TRANSFORMS)	Fingolimod	Subgroup	Age < 40	ARR	↓
			Previous exposure to DMTs	ARR	-
Barkhof 2014 [3] (TRANSFORMS)	Fingolimod	Subgroup	No prior exposure to DMTs	% brain volume change	↑
			EDSS ≤ 3.5	% brain volume change	↑
			Age < 40	% brain volume change	-
Khatri 2011 [4] (TRANSFORMS ext)	Fingolimod	Extension	Originally randomised to study DMT	ARR	↓
				MRI lesions	↑
				% brain volume change	↑
				Disability progression	-
Kappos 2015 [5] (FREEDOMS ext)	Fingolimod	Extension	Originally randomised to study DMT (1.25 mg)	ARR	↓
				MRI lesions	-
			Originally randomised to study DMT (0.5 mg)	ARR	-
				MRI lesions	↑
Radue2012 [6] (FREEDOMS)	Fingolimod	Subgroup	No prior exposure to DMTs	% brain volume change	↑
			EDSS ≤ 3.5	% brain volume change	-
Izquierdo 2014 [7]	Fingolimod	Extension	Originally randomised to study DMT	ARR	↑
Hutchinson 2009 [8] (AFFIRM, SENTINEL)	Natalizumab	Subgroup	Age < 40	ARR	↓
				Disability progression	↓
			EDSS ≤ 3.5	ARR	↓
				Disability progression	-
Putzki & Maurer 2010 [9]	Natalizumab	Subgroup	Disease duration ≤ 6 years	ARR	↓
Putzki & Buehler 2010 [10]	Natalizumab	Subgroup	Disease duration ≤ 6 years	ARR	↓
Kallweit 2012 [11]	Natalizumab		No prior exposure to DMTs	ARR	–
Butzkueven 2014 [12] (TOP)	Natalizumab		EDSS < 3	ARR	↓
			No prior exposure to DMTs	ARR	↓
Coles 2011 [13] (CAMMS223)	Alemtuzumab		Age < 31	ARR	↓
				Disability progression	↓
				Disability reduction	↑
			Disease duration < 1.3 years	ARR	↓
				Disability progression	↓
				Disability reduction	↑
			EDSS < 2	ARR	-
				Disability progression	↓

Abbreviations: ARR: annualised relapse rate; DMTs: disease modifying therapies; EDSS: Expanded Disability Status Scale; MRI: magnetic resonance imaging.
[a] During the initial 1 or 2 years on treatment, as per the definition of each study/study extension.

early vs. delayed treatment with high-efficacy agents and (iii) the effect of time from the MS diagnosis on the difference between the effectiveness of low- and high-efficacy therapies.

6.2. Limitations

Most of the reported data were derived from subgroup analyses of randomised clinical trials or their extensions. We believe that published trial durations are too short, in particular where confirmed disability progression events were reported. Informed censoring is also a considerable problem in the trial extensions, which could potentially be mitigated with "intention-to-treat" analytical approaches. Only a limited number of trials studied reduction of disability. In addition to the effect of therapy, regression to the mean and time-dependent decline in relapse activity both contribute to the decrease in relapse activity in study extensions. Comparing relative differences between treatment arms in subgroup analyses eliminates these potential confounders. Subgroup analyses have significant limitations, mainly due to the lack of power and the lack of comparability between the reported subgroups [50]. In addition, the reviewed publications did not report formal comparisons between the initial on-treatment activities recorded during the original trials vs. their extensions. Therefore, we refrain from reporting results of inferential statistics and instead provide a synthesis of the observed trends.

Participants in the different studies were recruited from mixed populations, based on differing definitions of prior disease activity and treatment status. As discussed above, underlying disease activity of the studied cohorts has an important impact on the relative benefit of high-efficacy therapies compared with more conservative therapeutic options. Therefore, part of the variability in the reported studies can be attributed to the differences in their inclusion criteria.

6.3. Conclusion

Based on the systematic review of literature, the evidence suggests that early treatment with high-efficacy DMTs offers an improved control of relapse activity when compared to the delayed therapy, although gaps in the data exist at the present time. This knowledge is mainly derived from extension studies and subgroup analyses of randomised clinical trials, as the direct evidence is at best limited. Therefore, further research is needed with the aim to answer the question of the timing of high-efficacy MS treatment directly. Evaluation of treatment safety and careful selection of patients who are most likely to benefit from early high-efficacy therapy or induction therapy is essential.

Take-home message

- Earlier treatment with high-efficacy, higher-risk therapies for relapsing-remitting multiple sclerosis leads to better control of relapse activity than their later initiation.
- The evidence regarding the effect of the timing of high-efficacy therapies on disability outcomes is conflicting and randomised trials or quality observational studies are required to answer this question.

Declaration of conflicting interests

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Helmut Butzkueven served on scientific advisory boards for Biogen, Novartis and Sanofi-Aventis and has received conference travel support from Novartis, Biogen and Sanofi Aventis. He serves on steering committees for trials conducted by Biogen and Novartis, and has received research support from Merck Serono, Novartis and Biogen.

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Author contributions

BM conducted the literature search, selected the relevant publications, summarised the published evidence, and drafted and revised the manuscript. HB, AT and EH contributed substantially to the interpretation of the results of literature search and the summary of the available evidence, and edited the manuscript. TK conceptualised the study, selected the relevant publications, summarised the published evidence and edited the manuscript.

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