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Review

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

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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

1. Introduction . . . 659
2. Methods . . . 659
   2.1. Search strategy and selection criteria . . . 659
3. Results of the literature search . . . 659
4. Defining early and delayed high-efficacy therapy . . . 659
5. Study outcomes of early vs. delayed treatment with high-efficacy DMTs . . . 659
   5.1. Fingolimod . . . 659
   5.2. Natalizumab . . . 661
   5.3. Alemtuzumab . . . 662
6. Discussion . . . 662
   6.1. Critical review of the literature . . . 662
   6.2. Limitations . . . 663
   6.3. Conclusion . . . 663
Take-home message . . . 663
Declaration of conflicting interests . . . 664

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

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Acknowledgements . . . 664
References . . . 664

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