



REVIEW

Immune Reconstitution Therapy or Continuous Immunosuppression for the Management of Active Relapsing–Remitting Multiple Sclerosis Patients? A Narrative Review

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ABSTRACT

The majority of disease-modifying drugs (DMDs) available for the management of active relapsing–remitting multiple sclerosis (RMS) depend on continuous drug intake for maintained efficacy, with escalation to a more active

drug when an unacceptable level of disease activity returns. Among continuously applied regimens, interferons and glatiramer acetate act as immunomodulators, while dimethyl fumarate, fingolimod, ocrelizumab, natalizumab and teriflunomide are associated with continuous immunosuppression. By contrast, immune reconstitution therapy (IRT) provides efficacy that outlasts a short course of treatment. Autologous hemopoietic stem cell transplantation is perhaps the classic example of IRT, but

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this invasive and intensive therapy has challenging side-effects. A short treatment course of a pharmacologic agent hypothesized to act as an IRT, such as Cladribine Tablets 3.5 mg/kg or alemtuzumab, can provide long-term suppression of MS disease activity, without need for continuous treatment (the anti-CD20 mechanism of ocrelizumab has the potential to act as an IRT, but is administered continuously, at 6-monthly intervals). Cladribine Tablets 3.5 mg/kg shows some selectivity in targeting adaptive immunity with a lesser effect on innate immunity. The introduction of IRT-like disease-modifying drugs (DMDs) challenges the traditional maintenance/escalation mode of treatment and raises new questions about how disease activity is measured. In this review, we consider a modern classification of DMDs for MS and its implications for the care of patients in the IRT era.

Keywords: Disease-modifying drug; Escalation therapy; Immune reconstitution therapy; Maintenance therapy; Multiple sclerosis

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Key Summary Points

The majority of disease-modifying drugs (DMDs) available for the management of multiple sclerosis (MS) depend on continuous drug intake for maintained efficacy, with escalation to a more active drug when an unacceptable level of disease activity returns.

Immune reconstitution therapy (IRT) provides efficacy that outlasts a short course of treatment.

Pharmacological IRT, currently Cladribine Tablets 3.5 mg/kg or alemtuzumab, can provide long-term suppression of MS disease activity, without need for continuous treatment.

Cladribine Tablets 3.5 mg/kg shows some selectivity in targeting adaptive immunity with a lesser effect on innate immunity.

The introduction of IRT-like disease-modifying drugs challenges the traditional maintenance/escalation mode of treatment and raises new questions about how disease activity is measured.

INTRODUCTION

The management of active relapsing–remitting multiple sclerosis (RMS) has been based traditionally on maintenance therapy in which the patient takes a given disease-modifying drug (DMD) continuously, with a return of relapses when the drug is discontinued [1]. This approach has brought success: more than two decades of therapeutic use of beta-interferons, for example, has reduced relapse rates and disease worsening across the MS population as a whole [2]. A DMD with higher efficacy may be needed in the event of breakthrough relapse(s), worsening of disability (escalation) or where MS is highly active at diagnosis. In the last decade, we have witnessed an impressive increase in the

availability of new DMDs for the management of RMS that are taking us beyond the age of maintenance/escalation therapy. Many of these are high-efficacy drugs, but their use is also accompanied by significant safety concerns and/or monitoring schemes that may be burdensome [3]. DMDs that act in the manner of an immune reconstitution therapy (IRT) have the potential to protect against relapses for years after a short course of treatment. In this review, we compare the therapeutic profiles of DMDs hypothesized to act like an IRT and the classical application of maintenance/escalation therapy in terms of their associated treatment burdens, MS outcomes and safety. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

CLASSIFICATION OF MS THERAPIES

Immunomodulation Versus Immunosuppression

Maintenance treatment for RMS includes immunosuppressants and immunomodulators (Table 1). Reduced efficacy or activity of the immune system, which is associated with significant lymphopenia during immunosuppression, may diminish immune responses to infectious agents or to vaccinations. In comparison, immunomodulators do not impair the overall activity of the immune system; rather, they interact in multiple ways with components of the immune system that are still incompletely understood. For example, interferon-beta inhibits the activation and proliferation of lymphocytes and the entry of lymphocytes into the central nervous system (CNS) [4]. This results in a shift in the balance of cytokine production from pro- to anti-inflammatory [4]. Glatiramer acetate, another immunomodulator, also reduces the net production of inflammatory cytokines via different mechanisms, including within the CNS [4].

The World Health Organization Collaborating Center for Drug Statistics has provided a classification of drugs that sheds some light on

their mechanisms of action (also included in Table 1) [5]. Most current maintenance therapies involve continuous administration (although maintenance treatment with ocrelizumab involves infusions at 6-monthly intervals). Some current maintenance therapies for RMS target lymphocytes to cause profound and continuous suppression of peripheral lymphocytes (e.g. fingolimod [6], dimethyl fumarate [7]), of lymphocytes within the CNS (natalizumab [8]) or of CD19+ lymphocytes (ocrelizumab [9]). Teriflunomide inhibits the response of the immune system to a stimulus [10], while the mechanism of action of dimethyl fumarate on immune function is complex [11]. Cladribine Tablets 3.5 mg/kg (refers in this article to Cladribine Tablets 10 mg, given to achieve 3.5 mg/kg cumulative dose over 2 years) and alemtuzumab act in different ways to the other DMDs in that list (see Fig. 1), as will be described in the following text.

Continuous immunosuppression has important functional consequences for the therapeutic use of these drugs, as this treatment has been associated with an increased risk of infections [12, 13] and, in some cases, increased risk of malignancy [14, 15]. The implications of these observations for individual DMDs, including those that act like IRTs, is described in the following sections.

Immune Reconstitution Therapy

Autologous Hematopoietic Stem Cell Transplantation

The key characteristic of an IRT is a long-lasting period of efficacy (however measured, see below) that follows an initial short course of treatment, without continued exposure to the drug. Autologous hematopoietic stem cell transplantation (aHSCT) provides a useful working definition of an IRT [16].

Briefly, in aHSCT HSCs are mobilized from the bone marrow and harvested, following which the patient's pathological immune system is ablated entirely using strong immunosuppressive drugs; subsequent reinfusion of the HSCs allows the immune system to rebuild, without further autoimmunity if the treatment

is successful [16, 17]. Clinical studies suggest that aHST is an effective treatment, with progression-free survival in 70–91% of patients, MRI event-free survival in 85–100% and “no evidence of disease activity” (NEDA) in 68–70%, at 4–5 years post-treatment [16]. The toxicity of aHST includes a low but measurable risk of treatment-related mortality, the possibility of prolonged hospitalization, viral reactivation and secondary autoimmunity and a probable impact on fertility [16]. Therefore, aHST is unsuitable for wide use.

The effects of aHST on immune cell populations appear to be more profound than those with any pharmacologic DMD [18]. However, DMDs with the characteristics of an IRT may present a more practicable alternative for most patients requiring high-efficacy therapy for MS [19–21]. Key therapeutic properties of these DMDs are summarized below.

Alemtuzumab

Alemtuzumab is administered over treatment periods consisting of five daily infusions followed by three daily infusions 1 year later [22]. One or two additional 3-day courses are supported if clinical MS events or MS events based on imaging criteria occur, with a minimum of 1 year between courses. Treatment with alemtuzumab rapidly and selectively removes about 95% of circulating lymphocytes [23]. The authors of a systematic review suggested that alemtuzumab reduces CD4+ and CD8+ T cells to a greater extent than does Cladribine Tablets, with a similar effect on B cells [18]. The molecular target of alemtuzumab, CD52 antigen, is also present on components of the innate immune system, including monocytes and dendritic cells, which are reduced in number following treatment with alemtuzumab [24–26]. The levels of these cells may recover over a period of about 6 months. Severe neutropenia is rare during treatment with alemtuzumab, however, and the extent of depletion of neutrophils is mild in most patients [27]. The nadir of lymphocyte count occurs at 1 month post-treatment; B cells recover over a period of about 3 months (and markedly overshoot the pretreatment value), while repopulation of T cells takes at least 1 year [23, 24]. In one study,

CD4 and CD8 counts were 30–40% of pretreatment values at 18 months after treatment [28].

The clinical benefits of alemtuzumab (reduced MS relapses and reduced disability) have been observed for up to a 5-year period of follow-up, without further DMD treatment [23, 28]. Accordingly, alemtuzumab acts like an IRT, with some effect on both the innate and adaptive immune systems (see Fig. 1). Indeed, an action on the innate immune system has been described as an important contributor to the efficacy of alemtuzumab [28]. Improved efficacy without additional safety concerns has been found with continuance of the second course of alemtuzumab when relapses occurred after the first course [29] and administration of additional courses of alemtuzumab when RMS disease activity continued after the second course [30].

Treatment with alemtuzumab is associated with an increased risk of bacterial infections (including listeriosis and tuberculosis [TB]), viral infections (herpes simplex and zoster and human papillomavirus) and fungal infections [31, 32]. The increased incidence of bacterial and fungal infections may be consistent with the drug's suppression of innate and adaptive immunity [33]. A high incidence of secondary autoimmunity, especially in the thyroid (where Graves' hyperthyroidism and Hashimoto thyroiditis account for about three-quarters of cases of thyroid dysfunction [34]) and platelets (which can cause immune thrombocytopenia), is believed to be associated with reconstitution of the lymphocytes [32, 35]. To date, there has been no clear signal for a general increase in the risk of malignancy with alemtuzumab, compared with other DMDs. The European labeling for the drug cites a risk of thyroid cancer associated with secondary autoimmunity [22], but it is unclear to what extent this was based on observation bias arising from increased monitoring of the thyroids of alemtuzumab-treated patients [36]. The US label for alemtuzumab identifies an elevated risk of lymphoproliferative disorders, lymphomas and malignant melanoma [37]. The long-term safety profile of alemtuzumab in a global safety database is consistent with the known tolerability and safety profiles of this agent [38]. At the time of

writing, the use of alemtuzumab has been restricted due to safety concerns, including severe neutropenia, immune-mediated reactions and adverse events in the cardiovascular system (such as pulmonary bleeding, stroke, myocardial infarction, cervicocephalic arterial dissection [39, 40]).

Cladribine Tablets 3.5 mg/kg

Cladribine Tablets 3.5 mg/kg is a relatively newly introduced management option for MS. Four sessions of treatment are required in total: two periods of 5 consecutive days of treatment are given 1 month apart at the initiation of treatment, which is repeated after 1 year [41]. The labeling also states that there is “no requirement” for further treatment for years 3 and 4.

A profound and almost complete reduction in B cells (CD19+) is observed within weeks of administration of Cladribine Tablets 3.5 mg/kg; recovery to the normal range is usually achieved at around 12 months post-treatment [42–44]. A more gradual, but incomplete, reduction, in CD4+ and CD8+ T cells occurs; CD4+ cells recover to the normal range in about 18 months, while CD8+ cells do not fall below the normal range. Mild-to-moderate reductions in neutrophil counts have been observed in about 25% of patients according to the US Prescribing Information [45]. Importantly, other cell types, including monocytes, are little affected by Cladribine Tablets 3.5 mg/kg, indicating a relatively minor effect on the innate immune system.

Clinical trials have demonstrated the efficacy of Cladribine Tablets 3.5 mg/kg over 2 years of follow-up in patients with RMS, including reductions in relapse rates, magnetic resonance imaging (MRI)-based disease activity and progression of disability [46–48]. Longer-term efficacy was observed in an extension to a clinical trial in RMS patients that involved a total of 4 years of follow-up [49, 50]. Importantly, in this extension study, relapse rates were similar for patients who continued to receive Cladribine Tablets 3.5 mg/kg and those who were re-randomized to placebo [49]. Overall, the short course of treatment and extended period of efficacy beyond the period of reduction in lymphocyte counts observed in many patients

is consistent with an IRT-like mechanism (Fig. 1) [17]. Treatment with Cladribine Tablets 3.5 mg/kg also reduced the rate of conversion to clinically definite MS over 2 years in patients with a first demyelinating event [51].

Treatment with Cladribine Tablets 3.5 mg/kg may be associated with reactivation of herpes zoster or TB, in particular in patients with profound lymphopenia (grade 3 or 4), as described in its labeling [41]. There has also been a recent case report of lichenoid rash associated with Cladribine Tablets in a single patient, which resolved with appropriate management [52].

The prescribing information describes a numerical increase in the risk of malignancy. A meta-analysis of 11 clinical trials performed with various DMDs demonstrated an unexpected absence of malignancy in the placebo group of the principal Phase 3 study of Cladribine Tablets, and this was significantly lower than that in the placebo groups of the trials of other DMDs. Moreover, in this meta-analysis, the incidence of malignancy was not higher for Cladribine Tablets 3.5 mg/kg compared to the other DMDs [53]. Epidemiological analyses based on the GLOBOCAN reference database support those findings, since they showed that Cladribine Tablets-treated subjects did not show an excess of malignancies compared with the general population, with a standardized incidence ratio for any cancer of 0.97 (95% confidence interval [CI] 0.44–1.85) for Cladribine Tablets 3.5 mg/kg and 0.48 (95% CI 0.14–1.53) for placebo [54]. An integrated analysis of clinical evaluations of Cladribine Tablets 3.5 mg/kg that included all patients who received this treatment revealed an excess risk of 0.20 events/100 patient-years (95% CI – 0.0785 to 0.3947) versus placebo, which was not statistically significant [55].

Ocrelizumab

The anti-CD20 mechanism of ocrelizumab has the potential to act like an immune reconstitution therapy, and ocrelizumab has been described in these terms [56]. However, this agent is given continuously, albeit with a long dosing interval of 6 months during maintenance treatment [57], consistent with the manner of its administration in its pivotal

Maintenance/escalation therapy		Immune reconstitution therapy-like action	
Immunostimulation/immunomodulation	Continuous immunosuppression	More selective ^a	Less selective ^a
Interferons Glatiramer acetate	Dimethyl fumarate Fingolimod Ocrelizumab Natalizumab Teriflunomide	Cladribine Tablets	Alemtuzumab

Fig. 1 Modern classification of disease-modifying drugs used in the management of active relapsing–remitting multiple sclerosis, with reference to the mechanism of action. ^aRefers to balance of effect on adaptive immunity and innate immunity, with “more selective” implying a greater effect on the former and a lesser effect on the latter.

clinical trials in persons with MS [9]. Ocrelizumab is effective in RMS, achieving reductions of 46–47% in relapse rates and reduced rates of disability progression, compared with interferon-beta [9]. However, it is not known whether the efficacy of ocrelizumab outlasts the period of its administration in the manner of other treatments hypothesized to act like an IRT [19]. Reviews in this area have described ocrelizumab as an agent which “might be either called a chronic immunosuppressive or pulsed immune reconstitution therapy” [19] or have placed this agent in a class of its own between maintenance therapy and IRT [20].

IMPLICATIONS FOR PATIENTS

Clinical Efficacy and Safety

The data summarized so far in this review show that available DMDs hypothesized to act like IRTs for RMS demonstrate durable efficacy. Although it is not possible to exclude an increased risk of malignancy with IRT-like DMDs at the present time, the data summarized above on malignancy rates for IRT-like drugs do not suggest a strong signal for increased risk of malignancy. There is clearly a need for further data on the potential of IRT-like DMDs for

Autologous hemopoietic stem cell transfusion is not included here, but would be considered to be a non-selective immune reconstitution therapy, as it involves ablation of the patient’s entire immune system (see text for details)

increasing the risk of malignancy, especially data on the newer agents. Such data take time to collect, and short-term trials are not designed or powered to assess this outcome. Ongoing registries can play an important role in defining the true long-term risk:benefit profiles of all DMDs, including alemtuzumab and Cladribine Tablets 3.5 mg/kg.

Burden of Treatment

A short course administration of a DMD is more convenient for patients than continuous treatment [21]. The use of IRT-like DMDs also effectively bypasses issues of adherence to therapy, which is known to influence outcomes in RMS [58]. Pretreatment with a corticosteroid is recommended for ocrelizumab [57] and alemtuzumab [22]. Additional pretreatment with an antihistamine is required for ocrelizumab, and an antipyretic recommended for both ocrelizumab and alemtuzumab [22, 57]. No pretreatment is required for Cladribine Tablets 3.5 mg/kg [41].

Monitoring burdens also vary greatly between treatments. Focusing on alemtuzumab, thyroid tests are required at 3-monthly intervals, and full differential blood counts, serum creatinine and microscopic urinalysis should be

Table 1 Brief overview of the action of disease-modifying therapies on the immune system

Disease-modifying therapies	World Health Organization classification	Effect on the immune system
Interferon-beta	Immunomodulating agent	Does not cause profound or continuous suppression of immune function
Glatiramer acetate	Immunostimulator	
Dimethyl fumarate	Other immunosuppressants	Complex mechanism involving decreased B-cell CD40 expression that is associated with disrupted B-cell activation, decreases in memory T-cells and T-cell proliferation and activation [7]. Causes lymphopenia
Teriflunomide	Selective immunosuppressant	Inhibits the expansion of lymphocyte numbers in response to a stimulus [10]
Fingolimod	Selective immunosuppressant	Continuous suppression of peripheral lymphocytes [6]
Natalizumab	Selective immunosuppressant	Acts as a compartmentalized immunosuppressant in the central nervous system only [8]
Ocrelizumab	Selective immunosuppressant	Inhibition of CD20 lymphocytes [9]
Alemtuzumab	Selective immunosuppressant	Actions consistent with a mechanism involving immune reconstitution ^a
Cladribine Tablets	Selective immunosuppressant	

^a See text for references

conducted monthly (in addition to measurements of each of these parameters before starting treatment) and continued for 4 years after the last treatment, according to European labeling [22]. The corresponding monitoring burden for Cladribine Tablets 3.5 mg/kg is lower. Blood counts must be performed before each treatment course in years 1 and 2 (with treatment given if values are $\geq 1000/\text{mm}^3$ and $800/\text{mm}^3$, respectively), and again 2 and 6 months after each treatment course (with additional monitoring needed only if blood counts are below these values) [41].

What We Don't Know—Issues for the Future

What to Measure?

With the increasing efficacy of treatments for RMS, attention is shifting from the use of

relapse rates as a marker of efficacy towards the use of NEDA as a treatment outcome [59–61]. NEDA is linked to both improved short-term patient outcomes and also to the prevention of long-term disability in MS. Ongoing research will define which of several versions of NEDA to use. NEDA-3 requires the observation of no new MRI-based events plus no disability progression, and NEDA-4 adds a measure of brain atrophy [60, 61]. “Minimal evidence of disease activity” (MEDA) has also been proposed as a treatment outcome in order to allow for a low level of MRI activity [61].

Substantial proportions of patients with RMS in analyses from recent trials have achieved NEDA for up to 2 years, including those in trials evaluating Cladribine Tablets 3.5 mg/kg (44 vs. 16% on placebo over 96 weeks in the CLARITY study [46, 62]), ocrelizumab (48 vs. 25–29% on interferon-beta-1a in the OPERA I and II trials [9, 63]) and alemtuzumab (39 vs. 27% and 32 vs.

14%, each compared with interferon-beta-a in the CARE MS I and CARE MS II trials, respectively [64, 65]). Other high-efficacy DMDs have also demonstrated high achievement of NEDA, such as natalizumab (37 vs. 7% on placebo in the AFFIRM study [66, 67]), fingolimod (33 vs. 13% on placebo in the FREEDOMS study [68, 69]), dimethyl fumarate (28 vs. 15% on placebo in the DEFINE study [70, 71]) and teriflunomide (23% in the TEMSO study [72, 73]). Accordingly, the use of NEDA as an outcome may influence the application of therapy in the IRT era. It has been suggested that while a relapse on maintenance/escalation therapy would lead to a switch to a higher-activity DMD, the re-emergence of disease activity in a patient receiving an IRT-like DMD may lead to further application of the same treatment before a switch [62].

Who to Treat with an IRT-like DMD?

The prospect of long-term remission of RMS with DMDs that resemble IRTs challenges the traditional escalation/maintenance treatment pathway of starting patients on a classical first-line agent and switching them to more active therapies only with relapse. A recent benefit:risk assessment of Cladribine tablets for patients with RMS, compared with other DMDs using a multi-criteria decision analysis model, confirmed the applicability of Cladribine Tablets for use in patients with RMS, especially for those with high disease activity [74]. The IRT approach provides an additional management option, especially for patients presenting with highly active disease: such patients now have the option of a trade-off between an increased risk of side-effects with a highly active therapy, such as an IRT, and the potential of greater long-term efficacy. The low treatment and monitoring burden of Cladribine Tablets 3.5 mg/kg may be an important factor in the choice of therapy for such patients.

CONCLUSIONS

The availability of DMDs that appear to act like an IRT is a major advance in the management of RMS. Many patients achieve long-term

remission of disease activity for several years, with a reduced treatment burden and without the potential of long-term continuous immunosuppression to promote malignancy. In addition, the short-course nature of DMDs that act like an IRT broadens the options for applying highly active therapy for RMS and facilitates individualization of therapy in accordance with individual patient preferences. Longer-term follow-up with any new agents is needed to better define their benefit:risk profile.

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