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Intensive immunosuppression in multiple sclerosis

Abstract Immunosuppressive drugs have been used out of label in multiple sclerosis (MS) for over 30 years and around 10% of patients are actually under immunosuppressive treatment. The rationale for immunosuppression in MS lies in the hypothesis that MS is an inflammatory immune-mediated disease that can take advantage of strong anti-inflammatory activity. Azathioprine, methotrexate, cyclophosphamide and mitoxantrone are the most utilised agents, but only the latter has been approved for clinically active MS. Many of them are safe in combination with interferon-β and are under investigation in controlled trials. Plasma exchange is limited to catastrophic attacks in refractory MS whilst bone marrow transplantation is considered in patients with an extremely severe, active disease as the final option in escalation therapy. Although immunosuppressants are best effective in induction therapy, their use is limited by toxicity and potential long-term risk.

Key words Immunosuppressive drugs • Induction therapy • Escalation therapy • Combined therapy • Rescue therapy • Multiple sclerosis

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Introduction

Immunosuppressive drugs have been used out of label for treating multiple sclerosis (MS) for over 30 years and even after interferon-β (IFN-β) and glatiramer acetate (GA) were approved as disease-modifying agents (DMAs), they are still in use. Around 10% of MS patients are treated with an immunosuppressant [1], mitoxantrone (MX) and cyclophosphamide (CTX) being the most widely employed in secondary progressive (SP) course. The rationale for treating MS with immunosuppressants lies in the concept of MS as an inflammatory immune-mediated disease with secondary axonal loss that is (at least in part) inflammation-dependent. Strong evidence suggests that the immune response in MS is Th1-type biased and that switching to Th2-type response may be beneficial. Thus, many therapeutical strategies deal with more or less selective interventions in the delicate equilibrium between molecules that operate in the immune response (antibodies, chemokines, adhesion and costimulatory molecules etc.) in order to "tune" the immune system toward a less detrimental response. As a matter of fact, the term "immunomodulatory" agents has been coined to distinguish such drugs from immunosuppressive drugs that are thought to non-selectively turn down all immune responses. This simplified vision does not reflect the complexity of both the immune system and MS: different pathological subtypes of disease have been recognised with different mechanisms of tissue damage [2], suggesting that MS may be a spectrum of diseases requiring different therapeutical approaches. On the other hand, immunosuppressants have different mechanisms of action with peculiar effects on the immune system that are of relevance in the treatment of selected forms of MS besides the registered DMAs.

Intensive immunosuppression in monotherapy

Azathioprine (AZA)

This antimetabolite of purines interferes with DNA synthesis of proliferating cells. A trend in favour of AZA for limiting MS progression comes from the only available placebo-controlled, randomised, double-blind study, on 98 SP patients [3], supported also by a meta-analysis of 793 patients [4]. Very recently, a positive effect on MRI endpoints has been reported [5]. AZA was never tested in patients with active, rapidly progressive MS but was found to be safe and well tolerated in combination with IFN-β (see later).

Methotrexate (MTX)

Similar considerations are valid for MTX, another antimetabolite that in addition decreases the expression of chemokines CXCR3 and CCR4 and the secretion of inflammatory cytokines [6]. A few trials investigated MTX in SPMS at low oral [7] or high i.v. doses [6], finding a mild effect of progression stabilisation. Although hepatotoxicity is a limiting side effect, available data suggest that MTX deserves further large controlled trials.

Cyclophosphamide

This alkylating agent interferes with rapidly expanding cells like leukocytes. Although originally used as a general immunosuppressant inducing T- and B-cell lymphopenia, CTX crosses the blood-brain barrier and induces a shift toward a Th2-type response [8]. Unfortunately, CTX is not under patent and there is not enough interest in conducting large clinical trials. CTX is prescribed with very variable treatment regimens, the most usual starting with i.v. pulses with 800 mg/m^2 monthly, then increasing the time intervals for 2–3 years. Bladder toxicity limits CTX use below a cumulative dose of 100 g and the risk of uncontrolled lymphopenia requires continuous monitoring and dose adjustment. CTX treatment seems effective in patients with early, aggressive MS with active, inflammatory disease [9] but not in those with a slowly progressive course [10].

Mitoxantrone

The anti-neoplastic agent MX shows a broad spectrum of action and peculiar immunosuppressive and immunomodulating properties [11]. Preliminary results suggesting a profound effect on clinical and MRI endpoints were confirmed in large, randomised, double-blind trials in patients with active, rapidly worsening MS [12, 13]. MX decreased relapse rate by 68–77% and progression of disability by 63–83%, and reduced the appearance of new T2 lesions at MRI and the finding of Gd-enhancing lesions by 86%. After these results, MX was the first immunosuppressant approved for the treatment of worsening relapsing-remitting (RR), SP and progressive relapsing MS. The two most commonly used regimens are 10–12 mg/m^2 i.v. every 3 months for 2 years or 20 mg i.v. combined with 1 g methylprednisolone i.v. every 4 weeks for 6 months. Although MX is generally well tolerated, its dose-dependent cardiotoxicity limits its use to cumulative doses lower than 140 mg/m^2. The risk of developing acute T-cell leukaemia should also be considered in the long term [14]. Similarly to CTX, it should probably be restricted to those patients with an aggressive disease at onset or those unresponsive to all other immunomodulating DMAs [15].

Plasma exchange and intravenous immunoglobulin G (IVIG)

IVIG contains anti-idiotypic antibodies that exert many immune functions: neutralising circulating auto-antibodies, down-regulating proinflammatory cytokines, shifting to Th2-type immune response, inhibiting phagocytosis of myelin and contrasting complement-mediated demyelination. Besides these promising potential effects, clinical trials with IVIG gave conflicting results and did not demonstrate any significant benefit in SPMS [16]. Several questions remain open, including optimal doses, timing and if IVIG can substitute plasma exchange in the treatment of very severe attacks of MS unresponsive to corticosteroids.

Autologous haematopoietic stem cell transplantation (AHSCT)

AHSCT was recently demonstrated to be effective in severe, refractory MS, as it can completely abrogate the inflammatory activity detectable by MRI [17]. Crucial steps of AHSCT are the mobilisation of haematopoietic stem cells in the peripheral blood with a very high dose of CTX (4 g/m^2) and the reinfusion of the graft after a conditioning regimen (usually the BEAM protocol). Although mobilisation with CTX may be therapeutical *per se*, autoreactive B cells remain in the CNS despite intensive immunosuppression, as AHSCT does not abrogate CSF oligoclonal bands. Moreover, brain atrophy seems to progress independently from inflammation also in transplanted MS patients [18]. Morbidity and mortality rates in this procedure are still considerable and mean that AHSCT should be performed in experienced centres for very selected cases of very active, refractory MS. For these reasons a comparison trial with MX has been started.

Immunosuppression in escalation and "rescue" therapy

Escalation therapy represents a therapeutical strategy based on a reasonable decision-making procedure in which drugs with the best risk/benefit ratio are first preferred and, if needed, drugs with increasing power and/or toxicity (but not necessarily more effective) are successively adopted. Accordingly, IFN-β and GA are the first-line treatment of MS, based on type A recommendation for RR and type B for a SP course. Most consensus groups agree that treatment should start as soon as possible to prevent disease progression but, as IFN-β and GA seem to have a limited efficacy in time, treatment failure may occur quickly. Although the definition of treatment failure of DMAs is still controversial, it was estimated that perhaps one-third of RRMS patients treated with DMAs become non-responders [19]. In this case, increasing the dosage or frequency of IFN-β injection (type B recommendation) may be one strategy whilst switching to IFN-β may be an option for patients assuming GA. Immunosuppressants can provide a treatment option for patients responding sub-optimally to DMAs but limited data are available to support this notion. Drugs like CTX or MX may be beneficial as "rescue" therapy, provided that they are not given too late in the course of MS, when inflammation has disappeared: in these cases, an MRI scan with single or triple dose Gd is helpful in detecting residual inflammatory activity. Whether immunomodulating treatment should be restored after short-lasting immunosuppression is still a matter of debate. Combination therapy, the new immunosuppressive drugs (Table 1) and AHSCT are the next steps of escalation therapy in selected patients.

Immunosuppression in combination therapy

The rationale of combining two or more drugs with different mechanisms of action but effective on the same disease lies in a documented synergistic effect with the possible advantage of reducing doses and side effects. The combination of an immunosuppressive drug and an immunomodulatory drug may be considered an alternative step of the escalation approach in the management of non-responders. So far, few uncontrolled studies have been done with inconclusive results about efficacy, but very informative safety data are now available for combining IFN-β with AZA, MX, CTX, MTX or mycophenolate mofetil, [reviewed in 20].

The decision to add-on a drug to another must be data-driven and new controlled clinical trials are necessary to define efficacy and the risk–benefit ratio in the long-term. Caution should be used, as two combined drugs might antagonise or induce unexpected side effects or complications. A paradigmatic example is the combination of IFN-β with natalizumab, which resulted in 2 cases of progressive multifocal leukoencephalopathy.

Intensive immunosuppression as induction therapy

Induction therapy is a much more aggressive approach to the treatment of MS. It encompasses short-lasting intensive immunosuppression followed by maintenance treatment with an immunomodulatory DMA, once clinical stabilisation has been obtained. This approach is based on the knowledge that long-term evolution of disease is predicted by early clinical presentation, course and MRI findings [21] and that inflammation in the brain, which is sensitive to immunoactive drugs, predominates in the initial stages. Thus, It should be adopted very early in the disease course or even at onset if negative clinical or MRI prognostic factors are present (Table 2) or if there is an atypical presentation (e.g., many Gd-enhancing or pseudotumoral lesions). Induction therapy is particularly recommended for the so-called malignant or fulminant or catastrophic MS, although

Table 1 Other, new immunosuppressive drugs for the treatment of MS

Class	Name	Actions and features
Antimetabolites	Mycophenolate mofetil	Oral, combination therapy
Immunophilin ligands	– Cyclosporin A – Tacrolimus – Sirolimus (Rapamicin)	Decrease IL-2 levels Neuroprotective/neurotoxic
Humanised monoclonal antibodies	– Alemtuzumab (Campath 1) – Natalizumab (Tysabri) – Daclizumab – Rituximab	– Anti-CD52 – Anti-α4 integrin – Anti-CD25 (IL-2R) – Anti-CD20 (B cells)
Antibiotics	Minocycline	Oral therapy
Hormones	Oestrogen	Transdermal therapy
Others	– Cladribine – CFTY720 – Teriflunomide – Laquinimod	Oral therapy

Table 2 Early negative prognostic factors in MS

Polyfocal presentation at onset
Cerebellar, motor or sphincteric symptoms at onset
Severe first attack
Persistent disability after the first attack
Short interval between the first two attacks
High relapse rate in the first years
Accumulating disability in the first years
Elevated MRI burden of disease at onset (number and volume of lesions, enhancing lesions)

definition is controversial, but 50% of such cases seem responsive to plasma exchange [22].

In clinical practice, MX is the most utilised drug for induction. A preliminary open-label experience in France provided support to new international trials with MX and IFN-β in sequence versus IFN-β alone in patients with recent diagnosis and negative prognostic factors [23]. Also alemtuzumab is currently being tested in induction therapy. Although the treatment of MS has become much more aggressive than a few years ago, validation with appropriate phase II–III clinical trials is warranted before induction therapy is introduced early in patients with RR course and long-term surveys are needed to confirm acceptable safety profiles.

Conclusions

Immunosuppressive drugs are an important resource in the treatment of MS but toxicity and long-term risk limit their use for long periods. Moreover, a criticism may rise from the theoretical consideration that widespread immunosuppression might affect also the so-called "protective autoimmunity", which plays a neuroprotective role in MS as well as in healthy subjects [24].

The use of immunosuppressants must be critically re-evaluated in the light of recent knowledge on MS pathogenesis, according to different stages and, perhaps, different types of disease being treated, only if inflammation is still documented by MRI. This concept may not be trivial in that intensive immunosuppression can be seen as an intensive "anti-inflammatory" therapy that may hamper axonal degeneration and halt irreversible damage in the CNS, thus preventing progression of disability.

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