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Alternatives to current disease-modifying treatment in MS: what do we need and what can we expect in the future?

Abstract Disease-modifying treatments (DMTs) for multiple sclerosis (MS) are now widely available, and their beneficial effects on relapse rates, magnetic resonance imaging outcomes and, in some cases, relapse-related disability have been shown in numerous clinical studies. However, as these treatments are only partially effective in halting the MS disease process, the search for improved treatment regimens and novel therapies must continue. Strategies to improve our therapeutic armamentarium have to take into account the different phases or parts of the pathogenesis of the disease. Available treatments address systemic immune dysfunction, blood-brain barrier permeability and the inflammatory process in the central nervous system. Currently, patients who fail to respond adequately to first-line DMTs are often considered as candidates for intensive immunosuppression with cytostatic agents or even autologous stem cell transplantation. However, new approaches are being developed. Combination therapies offer an alternative approach that may have considerable potential to improve therapeutic yield and, although likely to present considerable challenges in terms of trial design, this certainly seems to be a logical step forward in view of the complex pathology of MS. Several new drugs are also being developed with the aim of providing more effective, convenient and/or specific modulation of the inflammatory component of the disease. These treatments include humanised monoclonal antibodies such as the anti-VLA-4 antibody natalizumab, inhibitors of intracellular activation, signalling pathways and T-cell proliferation, and oral immunomodulators such as sirolimus, teriflunomide or statins. There remains, however, an urgent need for treatments that protect against demyelination and axonal loss, or promote remyelination/regeneration. Due to the chronicity of MS, the therapeutic window for neuroprotective agents is wider than that following stroke or acute spinal cord injury, and may therefore allow the use of some drugs that have proven disappointing in other situations. Novel potential neuroprotective agents such as α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid antagonists and ion-channel blockers will be entering Phase II trials in MS in the near future, and it is hoped that these agents will mark the start of a new era for DMTs for MS.

Key words multiple sclerosis · immunomodulators · monoclonal antibodies · neuroprotection

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Pathogenesis and available interventions

Multiple sclerosis (MS) is a heterogeneous disease with multiple neuropathological subtypes, and a variable genetic background that impacts on immune reactivity and the vulnerability and repair capacity of central nervous system (CNS) tissue. Furthermore, the role of autoimmunity/inflammation is complex, and may change over time and in different disease courses. There is also increasing evidence that a progressive neurodegenerative process takes place, which is only loosely (if at all) associated with the autoimmune attack, especially later in the disease evolution.

JON 1509

Three mechanisms of tissue injury – immunological, excitotoxic and metabolic – have been proposed to be involved in the pathogenesis of MS, and each of these represents a group of possible therapeutic targets. Immunological factors can be subdivided into antigen-specific (direct attack on neurons and axons by T-cells and antibodies) and antigen non-specific (indirect damage of neurons and axons by inflammatory mediators from the innate immune system; cytokine-mediated pathways of neurotoxicity; and inflammation-related release of toxic factors such as nitric oxide). Transmitters such as glutamate cause an influx of excitotoxins, such as calcium or sodium ions, and create free radicals. Metabolic factors, including mitochondrial dysfunction and oxidative or metabolic stress, may also play a role in the pathogenic process.

Strategies to improve the therapeutic armamentarium also have to take into account the different phases or mechanism of the pathogenesis of MS. There are three major components of MS pathogenesis that are targeted by the currently available therapies – systemic immune dysfunction, increased permeability of the blood-brain barrier, and changes in the CNS parenchyma (Table 1). However, there is now an urgent need for therapeutics targeted at protecting against demyelination and axonal loss, as well as those promoting remyelination/regeneration.

Disease-modifying treatments

Disease-modifying treatments (DMTs) for MS are now widely available. Their beneficial effects on relapse rates, relapse-related disability and magnetic resonance imaging (MRI) measures have been shown in numerous clinical studies [1–8]. These effects, which are more pronounced early in the course of the disease, are long-lasting and have no rebound effects. Their efficacy has been shown to be dependent on dose and dose frequency [9, 10], and there is good tolerability. Nevertheless, as all these treatments are only partially effective, there is a need for modified treatment regimens and the development of novel therapies.

Optimising therapy – currently available disease-modifying treatments

Switching between immunomodulatory agents

Although changing immunomodulatory agent could offer the physician another strategy for improving therapeutic outcome among patients whose treatment does not appear to be optimal, there is no conclusive evidence to date to support this approach. Despite observations from individual clinicians, which suggest that changing from one DMT to another may optimise therapy, data from well-designed, controlled clinical trials are still needed to validate this approach.

Intensive immunosuppression

Immunosuppressive agents such as mitoxantrone and, to a lesser extent, cyclophosphamide and cladribine (on MRI only) have shown short-term efficacy in active relapsing-remitting (RR)MS and, to a lower level, in secondary progressive (SP)MS [11, 12].

In the Mitoxantrone in Multiple Sclerosis (MIMS) study, 188 patients with worsening RRMS or SPMS received placebo or intravenous mitoxantrone every 3 months for 2 years [12]. The mitoxantrone groups experienced significant benefits compared with the placebo group in terms of change in Expanded Disability Status Scale (EDSS) score, confirmed EDSS progression, and proportion of relapse-free patients. However, it is important to note that the placebo group showed a very low rate of progression compared with the placebo groups

Table 1 Available and evolving interventions for multiple sclerosis (MS)

Component of MS pathogenesis		Available interventions	Evolving interventions
Systemic	Immune dysfunction	IFN β, glatiramer acetate, immunosuppression	Immunosuppression, natalizumab, CTLA4, sirolimus, FTY720, xaliproden, teriflunomide, mesopram, statins
Blood-brain barrier	Increased permeability/dysfunction	Steroids, IFN β (glatiramer acetate) immunosuppression	Natalizumab, CCR1 antagonists, metalloprotease-inhibitors
CNS	Inflammation	(IFN β) glatiramer acetate, immunosuppression	Immunosuppression, new immunomodulators, APL, vaccination
	Demyelination		Neuroprotectants
	Axonal loss		Neuroprotectants, AMPA-antagonists, Na^+ channel blockers, xaliproden
	Scar formation/gliosis		
	Remyelination/regeneration		Growth factors, pre-oligos

Interventions in parentheses indicate doubt over efficacy at the respective component of pathogenesis
AMPA α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; *APL* altered peptide ligand; *CNS* central nervous system; *IFN* interferon

from studies of interferon (IFN) β, suggesting that the MIMS population may be skewed towards patients with less aggressive disease [12].

As the effects of cytostatic agents also seem to be best in early aggressive disease with high inflammatory activity, the decision to treat using these drugs should be made as early as possible – something that physicians may be reluctant to do. Long-term toxicity (cumulative cardiotoxicity and the possibility that there may be rare links to secondary malignancies) is also a concern in relation to the use of mitoxantrone; however, studies of experimental autoimmune encephalitis (EAE) in animal models suggest that antagonists such as dexrazoxane may protect against the cardiotoxic effects and help to widen the therapeutic window of this cytostatic agent [13].

Experimental and clinical observations have indicated that high-dose immunosuppression followed by autologous stem cell transplantation (ASCT) can induce remissions in patients with MS [14]. However, ASCT has been associated with both short- and long-term toxicity, and a mortality rate of 6–8 % in high-risk cases [14].

The European Group for Blood and Marrow Transplantation (EBMT) has recently reported a comprehensive analysis of 85 patients (61 % female) with various forms of MS who were treated with ASCT [15]. The median age was 39 (20–58) years and the patients suffered from advanced disease, with a median EDSS score of 6.5 (4.5–8.5). The median interval from diagnosis to transplant was 7 (1–26) years and the median follow-up was 16 (3–59) months. At the last assessment, 69 % of patients were improved or stable, 11 % had unconfirmed progression, and 20 % had progressed or died, mainly as a result of the procedure. The proportion of patients with confirmed progression-free survival was 72 % at 3 years. However, due to the heterogeneous nature of the study population and the uncontrolled, non-blinded design of the study, these data are not conclusive.

Although ASCT is purely experimental at present, a controlled study is in progress to compare mitoxantrone with ASCT. It is hoped that the results will determine whether this procedure can offer the physician an alternative to immunosuppressive, cytostatic agents.

Drug combinations

If we take into account the complex pathology of MS, combination therapy seems to be a logical step forward. There are several prerequisites when choosing combinations of drugs: each drug should be at least partially effective; there should be a synergistic or at least additive mode of action, but the drugs should not have additive or compound toxicities; and the overall regimen should be convenient (this may involve simultaneous or consecutive [phase-adapted] application).

Combination therapy could be considered in patients not responding to monotherapy as expected. However, determining whether a patient has 'breakthrough disease', and therefore treatment is not optimal, is problematic. Alternatively, combination therapy could be used as the initial treatment among patients with rapid disease progression or, in the future, among those with negative prognostic indicators (clinical, MRI, genetic measures).

Drug combinations already used in daily practice include the use of steroids in addition to ongoing DMTs for the management of relapses. At the clinical trial stage, IFN β is being investigated in combination with:

- Periodic methylprednisolone pulses in 'breakthrough disease' [16, 17],
- Mild oral immunosuppressants (e. g. methotrexate [18] or azathioprine [19]),
- Intensive immunosuppressants (e. g. cyclophosphamide [20]).

Future promising combinations include IFN β-1a plus, ideally, an agent with a different mechanism of action such as an antioxidant [21–23]. Nevertheless, although combination therapy is theoretically an attractive approach to optimising treatment, it may be difficult to evaluate according to the principles of evidence-based medicine.

New agents with a more selective mode of action

Humanised monoclonal antibodies

Humanised monoclonal antibodies are among the novel therapeutic agents designed to target specific molecules at the immunological synapse. Those currently under investigation include:

- Anti-VLA-4 (natalizumab, which targets α4β1 integrin): Phase II positive, Phase III ongoing,
- CTLA4-Ig (BMS188667, structural homologue of CD28): Phase II interrupted,
- Daclizumab (targets the α-subunit of the high-affinity interleukin (IL)-2 receptor): Phase I/II,
- Alemtuzumab (targets the cell surface glycoprotein CD52): Phase II/III ongoing,
- Anti-CD20 (rituximab): Phase I,
- Anti-CD40L/-CD154 (IDEC-131): Phase I,
- Anti-IL-12 (J695): Phase I/II.

The most advanced of these is the humanised α4 integrin antagonist natalizumab. Within the vasculature, α4 integrin antagonists prevent the recruitment and trafficking of α4-expressing leukocytes across vascular endothelium and into the CNS, by blocking interactions with the endothelial cell surface receptors, vascular cell adhesion molecule (VCAM)-1 and mucosal adressin cell

adhesion molecule (MAdCAM)-1, potentially ameliorating inflammation [24].

In a recent randomised, double-blind trial, patients with RRMS or relapsing SPMS received intravenous natalizumab or placebo every 28 days for 6 months [24]. There were pronounced reductions in the mean number of new enhancing lesions and relapse rate among patients receiving natalizumab compared with those receiving placebo. However, natalizumab showed limited activity, with inflammation and relapses resuming 1 or 2 months after the treatment was stopped, suggesting that continued dosing is required to maintain the beneficial effect. Safety data are so far available only from Phase II trials in MS and Crohn's disease, and represent limited exposure in terms of patient numbers and treatment duration [24, 25]. However, two large Phase III clinical trials are ongoing to investigate this and whether the continued use of natalizumab, either in mono- or combination therapy, is associated with a reduction in effect.

Inhibitors of intracellular activation, signalling pathways and T-cell proliferation

Another potential therapeutic avenue involves the use of inhibitors to block intracellular activation, signalling pathways and T-cell proliferation. Although these agents may not be as specific as monoclonal antibodies, they have the potential to target particular pathways involved in MS. Several novel drugs are in preclinical development, including:

- Inhibitors of signalling protein kinases (targeting several activation cascades)
  - lymphocyte-specific cytoplasmic protein-tyrosine kinase P56lck (Lck)
  - zeta-associated protein (ZAP)-70
  - protein kinase C theta
  - mitogen-activated protein kinase
- Inhibitors of calcium release-activated Ca-channel,
- Nuclear factor of activated T-cells,
- Inhibitors of Janus protein tyrosine kinase (JAK 3),
- Antimetabolites
  - inhibitors of pyrimidine biosynthesis – gemcitabine, leflunomide and FK778
  - inosine monophosphate dehydrogenase inhibitor – VX-497.

New oral immunomodulators/suppressants

Several oral immunomodulators are in Phase II/III studies, some of which are reviewed below.

Teriflunomide is a *de novo* pyrimidine synthesis inhibitor with antiproliferative activity. It is the active metabolite of leflunomide, which is used in the treatment of rheumatoid arthritis. Evidence from studies of EAE and, more recently, one Phase II clinical trial suggest that teriflunomide acts as an immunomodulator in MS [26].

CCI-779 is an ester of sirolimus that acts, in part, by binding to an intracellular cytoplasmic protein, FKBP12 [27]. This CCI-779:FKBP12 complex then binds to a cell cycle regulatory protein, mammalian target of rapamycin (mTOR), inhibiting its activation and suppressing cytokine (IL-2)-driven cell proliferation. By blocking T-cell proliferation, CCI-779 has the potential to suppress the immune responses believed to be key in autoimmune diseases such as MS. Furthermore, through its properties as a neuroimmunophilin ligand, CCI-779 may also have neuroprotective and/or neuroregenerative activities.

FTY720 is the first of a new class of immunosuppressants with a unique mode of action. Structurally similar to natural sphingolipids, it inhibits T-cell recirculation by activating sphingosine 1-phosphate G-protein-coupled receptors which, in turn, leads to the increased sequestering of T-cells into the lymph nodes. FTY720 has no effect on T-cell activation or expansion at clinically relevant doses. Moreover, the preventative and therapeutic effects of oral FTY720 monotherapy that have been shown in various models of EAE [28] and its ability to penetrate the blood-brain barrier make it an attractive candidate for use in the treatment of MS.

Xaliproden exhibits immunomodulating activity, inhibiting the synthesis of tumour necrosis factor-α and other cytokines, and neurotrophic properties. Originally developed for use in the treatment of patients with neurodegenerative diseases, it has been shown to abrogate EAE and protect against disruption of the blood-brain barrier [29].

Statins are cholesterol-lowering drugs that also appear to have some anti-inflammatory effects. *In vitro* experiments indicate that statins, such as simvastatin, lovastatin and mevastatin, can act to decrease the migration of activated T-cells, and also induce a T-helper cell cytokine shift [30]. An initial open-label, single-arm study of simvastatin therapy in 27 patients with RRMS has shown significant benefits in terms of reduction in the number and volume of Gd-enhancing lesions seen on MRI [31].

Other agents undergoing Phase II studies include: chemokine receptor-1 antagonists [32] and mesopram – a phosphodiesterase inhibitor [33].

Neuroprotective agents

Neurodegeneration may occur at any stage of the MS disease process. Therefore, the need to protect the CNS against demyelination and axonal degradation, in addition to addressing the inflammatory process at the earliest stage possible, is apparent.

Potential targets for novel neuroprotective agents include the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainate-type glutamate receptors. AMPA/kainate-type receptors mediate the toxicity induced by glutamate. During inflammation in both EAE and MS, lymphocytes, brain microglia and macrophages release excessive amounts of glutamate, which can then activate AMPA receptors (Fig. 1) [34]. This prolonged excitatory neurotransmission of glutamate can lead to neuronal damage – glutamate excitotoxicity.

AMPA/kainate receptor antagonists, for example talampanel and E2007, can ameliorate EAE in rodents, preventing clinical relapses and reducing axonal damage [35, 36]. These effects do not appear to be related to immunomodulation or anti-inflammatory actions [34]. Phase I and II studies have already been conducted in other neurological indications (e. g. stroke and epilepsy), but with unconvincing efficacy. The rapid implementation of Phase II/III studies in MS is feasible, although there are methodological challenges to be overcome before proof-of-concept studies can begin.

Riluzole is an inhibitor of glutamate transmission that is thought to act via pre-synaptic calcium channel blockade [37], and is currently used as a treatment for amyotrophic lateral sclerosis. In recent studies of EAE in animal models, riluzole appeared to reduce focal inflammation, demyelination and axonal disruption [38]. The results of a pilot study in 16 patients with primary progressive MS did not show any benefits in terms of disability; however, improvements were seen on some MRI measures [39].

Inhibitors of metabolic toxicity

Anticonvulsant drugs such as phenytoin and lamotrigine do appear to be at least partially effective in the treatment of some forms of neuropathic pain [40]. These drugs act primarily by reducing sodium conductance, increasing post-synaptic γ-aminobutyric acid-mediated inhibition and reducing pre-synaptic calcium entry. *In vivo* damage of CNS myelin and axons can be induced by peroxynitrite [41], and nitric oxide donors have shown to reversibly block axonal conduction, particularly in demyelinated axons [42]. However, recent experiments have suggested that sodium channel blockers and inhibitors of sodium/calcium exchange may protect axons from nitric oxide-mediated damage [43]. In EAE models, phenytoin treatment helps to protect spinal cord axons and preserves axonal function/conductance [44] but, as yet, results from clinical trials in MS are not available.

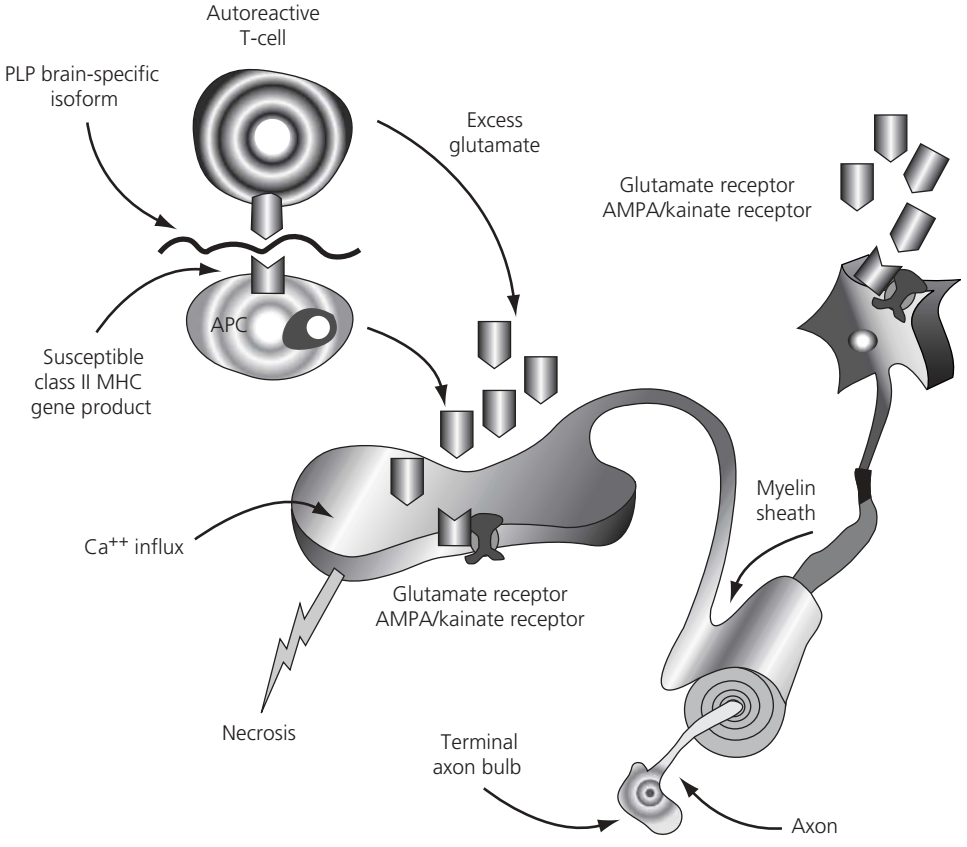

Fig. 1 Possible role of AMPA/kainate receptors in demyelination and axonal loss. From Steinman L (2000) Multiple approaches to multiple sclerosis. Nat Med 6:15–16 [34], and published with permission from the Nature Publishing Group. *AMPA* α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; *APC* antigen-presenting cell; *MHC* major histocompatibility complex; *PLP* proteolipid protein

Other potential inhibitors of metabolic toxicity in MS include antioxidants. Free radical generation by macrophages has been implicated in the demyelination and axonal degeneration that are seen in MS [45–47]. Antioxidants, such as alpha lipoic acid and tirilazade mesylate, have shown promising results in animals with EAE [48, 49]. However, trials of dietary antioxidants such as vitamin E or selenium in patients with MS have, so far, failed to show an effect, leading to suggestions that the effectiveness of such treatments may be related to whether or not they are able to permeate the blood-brain barrier [50]. A combination of IFN β plus vitamin B12 has been found to be effective in EAE [21], and the use of antioxidants in combination with IFN β is being investigated in a variety of indications [22, 23].

Conclusions

Although there is now a wealth of different clinical approaches and DMTs (Table 1), establishing better guidance for clinical decisions will be crucial for further advances in the day-to-day management of patients with MS. Promising directions include the use of clinical, imaging, pharmacogenomic and transcriptomic databases to develop prognostic profiles, which can be readily accessed by neurologists and used as decision-making tools in the initiation and optimisation of treatment.

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