Advances in Treating Multiple Sclerosis

a report by
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The approval of three interferons-beta (IFNβ) and of glatiramer acetate (GA) by the US Food and Drug Administration (FDA) in the early 1990s was the most important recent advance in multiple sclerosis (MS) therapy. These immunomodulators are now a first-line treatment of relapsing-remitting (RR) and relapsing-progressive (RP) MS. In 2000, mitoxantrone – a cytolytic immunosuppressant – was approved for the treatment of patients with a rapidly progressive disease. A second immunosuppressant – natalizumab (Tysabri®) – was approved in November 2004. Given its remarkable efficacy, natalizumab appeared a promising candidate for the long-term treatment of RR MS. However, severe adverse events led to a temporary suspension of the drug (February 2005 to June 2006). After its reintroduction to the market, natalizumab was reserved for carefully selected patients under strict surveillance and for a limited period of time. Immunomodulators are well tolerated for years, but their efficacy is relatively modest. Immunosuppressants are more effective, but their toxicity prevents long-term treatments. Numerous clinical trials investigate new molecules in order to improve the efficacy of immunomodulators and reduce the toxicity of immunosuppressants. This short review will be limited to the most promising new therapeutic approaches.

Approved Therapies

Immunomodulators

Interferons-beta

IFNβ downregulates T-cell proliferation and pro-inflammatory cytokine production. Their most evident anti-inflammatory effect concerns active brain lesions, demonstrated by a ~80–90% decrease of gadolinium-enhancing (Gd+) lesions. The clinical benefit on relapses is definitely less marked (~30%), and the long-term effect on disability progression is modest (~20%) and remains a matter of debate.

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Three formulations of IFNβ are available: IFNβ 1b (Betaferon®), IFNβ 1a im (Avonex®) and IFNβ 1a sc (Rebif®). So far, a marked superiority of their respective clinical benefit has not been demonstrated. The main difference concerns their immunogenicity leading to the production of neutralising antibodies (NAbs).[1,2] Interferonβ 1a im is less immunogenic, in part because of a less frequent administration (once a week) and/or the mode of injection (intramuscular). NAbs inhibit IFNβ biological activity and are associated with a decreased radiological and clinical benefit, apparent 6–12 months after their detection. Their clinical relevance, however, is not clearly defined as their titres vary over time and do not persist in some patients. The detection of NAbs titres of at least 20 at several-month intervals could identify 'non-reverter' patients.

Several attempts to improve IFNβ efficacy are in progress. A benefit of higher doses has been found with IFNβ 1b (500 versus 250µg) and IFNβ 1a sc (44 versus 22µg).[3] In contrast, a higher dose of IFNβ 1a im (60 versus 30µg) did not improve the benefit and led to a greater incidence of NAbs.[4] An increased formulation purity of IFNβ 1a sc is currently being tested. Preliminary data demonstrate a much lower persistence of NAbs and a three-fold reduction of adverse events.[5] A potential increased clinical benefit remains to be assessed.

Glatiramer Acetate (Copaxon®)

GA is a mixture of four synthetic polypeptides participating in the structure of myelin basic protein (MBP), which plays a major role in the development of allergic experimental encephalomyelitis (EAE). The most likely mechanisms of action are competition with MBP in binding to the major histocompatibility complex (MHC) molecule – acting as an altered peptide ligand – and the induction of GA-reactive T regulatory cells producing brain-derived neurotrophic factor. GA exerts beneficial effects on relapse rate and disability progression at a magnitude comparable to that of IFNβ. The first magnetic resonance imaging (MRI) studies demonstrated a reduction in Gd+ lesions by 33% – less than that with IFNβ. Tolerance is acceptable, but some patients present systemic reactions specific to GA characterised by flushing, chest pain, anxiety, dyspnoea and constriction of the throat, usually resolving within half an hour. To improve the efficacy of GA, higher doses have recently been tested (40 versus 20mg). Preliminary data suggest that a double dose may be more effective in reducing MRI activity and relapse rate, with a similar tolerance.[6]

Immunosuppressors

Mitoxantrone (Novantrone®)

Approved in 2000 by the FDA, mitoxantrone (MX) is a rescue therapy for patients with aggressive MS characterised by frequent and/or severely disabling relapses leading to rapidly progressive disability, who failed to respond to approved immunomodulators. MX is a cytolytic immuno-

suppressor acting on intracellular ligands with an exceptionally long terminal half-life. In addition, it is sequestered for weeks in deep tissues and slowly released. Immunocompetent cells are thus exposed to MX for long periods of time, which explains the efficacy of quite low doses (12mg/m^2) administered as infrequently as once every three months. Importantly, MX exerts immunosuppressive effects on both cellular and humoral parts of the immune system. In addition to the inhibition of antigen- and non-antigen-specific proliferation of activated T cells, B cells and dendritic cells, a selective and long-persisting decrease in B lymphocytes and antibody production is consistently observed.

It has come to be accepted that MX provides an effective treatment in most acutely worsening MS patients who do not respond to IFNβ or GA.[7] The best responders to MX therapy are patients with an RR course, more than three relapses in the previous 24 months and at least one Gd+ lesion.[8] Two important issues can be addressed: the most effective and least toxic treatment regimen, and the optimal maintenance therapy. The eradication of Gd+ lesions within three months of monthly infusions versus six months after quarterly administration favours a treatment regimen combining an induction phase of three monthly infusions followed by administration every three months as a maintenance therapy. The cardiotoxicity of MX is a major dose-limiting factor. Cumulative doses over 140mg/m^2 can lead to severe and irreversible myocardial dysfunction. However, there is a growing appreciation that cardiotoxicity can occur at lower cumulative doses. The FDA has thus recently updated its warnings and recommends a control of the left ventricular ejection fraction (LVEF) before every dose. Another concern about MX toxicity is the delayed occurrence of therapeutic-related acute leukaemia (TRAL). It is difficult to correctly appreciate the risk of TRAL, as the exact number of MS patients exposed to MX is unknown and cases of TRAL can be subject to under-reporting. According to the data from two prospective post-marketing studies[9,10] on a total of 1,311 patients, the incidence is between 0.20 and 0.25%. However, 19 sporadic cases have been reported in the literature with a worrying incidence in two centres of 2.7% (3/111 patients)[11] and 0.8% (2/250 patients).[12]

Natalizumab (Tysabri®)

Natalizumab, an immunosuppressor acting on cell-surface ligands, is a humanised monoclonal antibody targeting the α4 integrin chain of the VLA-4 adhesion molecule involved in transendothelial cell migration of immunocompetent cells into brain parenchyma. Leukocyte and lymphocyte counts in peripheral blood remain unaltered. In contrast, all lymphocyte subtypes are significantly reduced in the cerebrospinal fluid (CSF), likely mirroring reduced brain infiltration. In RR MS patients, natalizumab reduces Gd+ lesions by 92%.[13] The benefit seems better than after administration of IFNβ or GA; this also applies to relapses (relative risk reduction (RRR) 68 versus 33%) and disability progression (RRR 42 versus ~20%). Unfortunately, two out of 1,216 patients treated with natalizumab experienced progressive multifocal leucoencephlopathy (PML) – a JC virus infection. Even though both of these patients were participating in the trial combining IFNβ and natalizumab,[14] it seems unlikely that IFNβ contributed to the onset of PML.

> It has come to be accepted that mitoxantrone provides an effective treatment in most acutely worsening multiple sclerosis patients who do not respond to interferons-beta or glatiramer acetate.

> It has been observed in animal experiments that Fingolimod strongly reduces transmigration of macrophages into brain parenchyma.

There is no definite explanation concerning the emergence of PML in MS patients treated with natalizumab. However, neutralising VLA-4 may have unpredictable consequences, as this molecule has other important functions. Notably, VLA-4 plays a role in the formation of the immune synapse and in the cell interaction between CD8 cytotoxic T cells and their target. Interestingly, natalizumab administration leads to a net decrease of the CD4/CD8 ratio in the CSF[15] similar to that observed in HIV-infected patients, of whom 5% develop PML. CD4 cells play an important role in the control of JC virus and their reduction in the CSF may put MS patients at an increased risk. On the other hand, natalizumab favours the release of bone-marrow cells and possibly of those harbouring JC virus. Finally, the physiological trafficking of lymphocytes from blood to CSF and brain parenchyma represents the essential immunosurveillance that is possibly impaired by natalizumab.

Experimental Therapies

FTY720 (Fingolimod®)

Fingolimod® converts endogenous sphingosine into its phosphate form, which is a high-affinity agonist of the sphingosine 1 (S1P1) receptor. Fingolimod first accelerates homing of lymphocytes to lymph nodes and then blocks egress of lymphocytes from lymphoid tissues. The lymphocyte sequestration in lymphoid tissues leads to a major decrease in T- and particularly B-cell count (25% of baseline values) in peripheral blood. Fingolimod also causes thymocyte apoptosis, inhibits vascular endothelial growth factor (VEGF)-induced brain capillary leakage, impairs dendritic cell trafficking and induces a shift from Th1 (pro-inflammatory) to Th2 (anti-inflammatory) cytokine production. It has been observed in animal experiments that Fingolimod strongly reduces transmigration of macrophages into brain parenchyma.

In a preliminary phase II trial in RR MS patients,[16] a marked reduction in the relapse rate and Gd+ lesions was demonstrated at months 12 and 18. The most frequent side effects were infection and increased blood pressure. Bradycardia is commonly observed within six hours of the first administration, but disappears with continued treatment. It is too early to fully appreciate the future interest of this immunosuppressant in MS, given its potential long-term toxicity. One case of reversible posterior encephalopathy with a residual homonymous hemianopsia was reported. It is of note that other safety issues – such as macular oedema and pulmonary complications – led

to the discontinuation of clinical trials combining Fingolimod with other immunosuppressants. Combination therapies with Fingolimod should thus be considered cautiously.

Rituximab

Rituximab is a monoclonal Ab binding to the CD20 surface molecule that induces a selective, long-lasting depletion of B cells that is only partially reconstituted after one year. B cells play an important role in humoral immune mechanisms, which seem to predominate in certain MS phenotypes such as Marburg's and Devic's diseases, in which rituximab provided a substantial improvement. Rituximab has been rarely administered to MS patients, but recent trials in a small number of patients with the RR type suggest a positive effect on relapses and Gd+ lesions. Unfortunately, like other immunosuppressants, rituximab exposes patients to potential adverse reactions and the FDA has recently reported 21 patients with PML after rituximab therapy for haematological malignancies.

BBR2778 (Pixantrone®)

Pixantrone® is an analogue of MX without severe cardiotoxicity. In addition, its weaker DNA-constant binding and its lower stimulation of topoisomerase II-mediated DNA alterations suggest a lower risk of TRAL. In animal experiments, pixantrone was found to be less cardiotoxic than MX, and its immunosuppressive activity on the cellular and humoral components of the immune system is the same as that of MX. This new molecule might thus be an interesting substitute for MX in MS patients, and a phase I/II trial is in progress.

Alemtuzumab (Campath-1H®)

Alemtuzumab, a monoclonal Ab targeting the surface CD52 molecule

> Rituximab has been rarely administered to multiple sclerosis patients, but recent trials in a small number of patients with the relapsing-remitting type suggest a positive effect on relapses and gadolinium-enhancing lesions.

mainly expressed on T lymphocytes and monocytes, is a potent and selective immunosuppressant of cellular immunity leading to a complete deletion of lymphocytes. Monocytes and B cells return to normal within three months, but T-cell depletion persists for up to five years. Administration of alemtuzumab early after disease onset (mean disease duration 2.7 years) not only stopped relapses but also yielded a definite reduction in disability state over two years.[17] These observations suggest that a very early suppression of the inflammatory environment likely reduces the production of microglial toxic factors and the early concomitant axonal loss. The main side effect of alemtuzumab is a cytokine-release syndrome requiring pre-treatment with corticosteroids. The development of autoimmunity after alemtuzumab administration is another concern, leading to Graves' disease in 27% of treated patients and, less frequently, to Goodpasture's syndrome.

> The main side effect of alemtuzumab is a cytokine-release syndrome requiring pre-treatment with corticosteroids.

Conclusions

The overall benefit of INFβ and GA is modest. Nevertheless, given their acceptable tolerance there is ample evidence to recommend early and continuous treatment with one of these immunomodulators in order to delay the conversion of patients from the clinical isolated syndrome to confirmed MS and the shift from the RR to the secondary-progressive (SP) phase. Mitoxantrone can block disease evolution in most patients with breakthrough MS. Long-term tolerance appears acceptable when properly administered. Adverse cardiac events can be avoided with careful monitoring of myocardial functions. However, cardiotoxicity remains a strict dose-limiting factor and there is no clear therapeutic strategy so far to maintain the benefit after an effective MX immunosuppression. After a temporary suspension of alemtuzumab (February 2005 to June 2006), the FDA recommended its return to market. Given that the mechanisms responsible for PML occurrence are unknown and that there is no cure for PML, careful patient selection and monitoring according to recent recommendations are essential before starting treatment.[18] Several experimental therapies appear promising, but the follow-up is too short to fully appreciate their long-term toxicity. ■

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