REVIEW ARTICLE

Future Directions in the Treatment of Multiple Sclerosis

Havrdová E., Horáková D., Kovářová I., Krasulová E.
Department of Neurology, Charles University, 1st Faculty of Medicine and General Teaching Hospital, Prague, Czech Republic

SUMMARY

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system. A role in its pathogenesis is played by inflammatory and neurodegenerative mechanisms leading to myelin sheath destruction and irreversible nerve fibre loss. At present our therapy is largely confined to the inflammatory component, and only early initiation of therapy can effectively delay development of irreversible disability.
High-dose corticosteroids remain the "gold standard" in managing MS attacks.
Interferon beta and glatiramer acetate represent disease-modifying drugs. Both of these drugs reduce the incidence of attacks by about 30%; however, individual patient responsiveness is variable. Many patients experience further attacks requiring escalation of therapy, i. e., addition of immunosuppressives, combination with pulse steroid and cytostatic treatment. Intravenous immunoglobulins represent second-line treatment. In the case of rapid disease progression, immunoablation and stem cells transplantation are available.
The most successful recently tested drug was the monoclonal antibody natalizumab. Unfortunately, its use has been stopped for the time being because of serious adverse effects in patients treated with a combination of interferon beta and natalizumab. Monoclonal antibodies against interleukin-12 and chemokine receptor CCR2, and the cytostatics fumarate, laquinimod and cladribine are currently undergoing clinical trials. DNA vaccination is a revolutionary opportunity of inducing tolerance against myelin autoantigens.
Key words: multiple sclerosis, corticosteroids, immunosuppressives, cytostatics, intravenous immunoglobulins, immunoablation, monoclonal antibodies, DNA vaccination.

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HISTORICAL BACKGROUND

Multiple sclerosis (MS) is an autoimmune disease involving the central nervous system (CNS). The target antigens are those of the myelin sheath, i. e., of the white matter of the CNS. However, MS is not only associated with demyelination (myelin destruction) but, more importantly, with loss of nerve fibres, which are actually responsible for function in the nervous system (1). While myelin is capable of regeneration (remyelination) under certain circumstances, axonal loss is irreversible.

A role in the pathogenesis of MS is played by both inflammatory and neurodegenerative mechanisms, with intra-individual variability among patients.

Current therapy is primarily aimed at inflammation. Drugs effectively modulating the degenerative component of the pathogenesis of MS are not available at the moment.

The basic therapeutic option used to manage acute neurological symptoms (so-called attacks) is high-dose intravenous corticosteroids. Corticosteroids started to be used in the late 1960s and were long regarded as only a symptomatic therapy. Today we know their timely administration helps protect the damaged tissue (2) and their multiple administration slows the rate of brain atrophy, which is higher in MS patients compared with their healthy controls (3).

In the 1970s to 1980s numerous trials were conducted in cytotoxic agents, primarily with cyclophosphamide, azathioprine and methotrexate. While a host of these trials did demonstrate some effect of these agents, the trials had a number of methodological limitations as seen from todays perspective. The technique of patient selection for clinical trials, blinded technique, objective controls (currently represented by monitoring using magnetic resonance imaging, MRI) were not consistent with currently established criteria for clinical trials in MS. As a result, many of the above agents are undergoing new clinical trials.

In 1993 the first interferon beta was approved for clinical use; it has been shown to be able to affect the natural course of remitting MS. The management of MS entered a new era. The effect of interferon beta is non-specifically immunomodulatory. It acts primarily against interferon gamma, a product of activated lymphocytes; an integral part of the effect of interferon beta is its antiproliferative action. Glatiramer acetate was approved for the same indication in 1996. The structure of this molecule of copolymer of four repeating amino acids is similar to that of a myelin antigen and acts as a "false" antigen. Its recognition by T-lymphocytes is not followed by development of a subpopulation of Th1-lymphocytes, which play a pivotal role in the pathogenesis of MS, but the development of a subpopulation of Th2 instead. Although the mode of action is completely different, both drugs result in a decrease in the incidence of acute attacks by some 30%. The effect on the development of disability is less marked. The effect of these drugs is clearly most powerful if therapy is initiated in the earliest possible stage of the disease. Response by patients to these "drugs of first choice"

Address for correspondence:
Assoc. Prof. Eva Havrdová, MD.
Department of Neurology, 1st Faculty of Medicine, Charles University
128 21 Prague 2, Kateřinská 30
Czech Republic
E-mail: ehavr@lf1.cuni.cz

varies largely, with some patients showing an excellent response while the drugs fail completely in a minority of patients (4).

CURRENT PRACTICE

In the Czech Republic, the first drugs of choice for the treatment of MS were introduced between the years 1996-9. In 1996 the Czech Society of Neurology of the Czech Medical Association JEP developed very stringent criteria for patient selection, taking into account primarily disease activity as shown by the number of attacks. To date, efforts to make these criteria less rigid - so as to be consistent with those in effect in the European Union - have failed. At-risk patients are likewise not treated after their first attack of the disease; not for medical reasons (it is a well-known fact that disability is most likely in such patients), but for economic reasons.

Should the patient using drugs of first choice experience further attacks, their management is escalated through a combination with pulses of steroids, through addition of immunosuppressives (azathioprine, methotrexate, oral mycophenolate mofetil), or alternatively, through a combination of pulses of cytotoxic agents and steroids (cyclophosphamide and methylprednisolone, mitoxantron and methylprednisolone). Patients not tolerating drugs of first choice are switched to intravenous immunoglobulins (5).

Once full disability has developed, any therapeutic management is difficult as many of the axons required have been lost. The therapeutic regimen includes pulses of steroids or those of cytotoxic agents and steroids. The patient has to be protected from side effects, and therapy should not be prolonged if ineffective. Pulses of high-dose methotrexate have been tested in patients showing very rapid progression despite failure of conventional therapy. The most intensive therapeutic option is immunoablation with subsequent autologous hematopoietic stem cell support (6).

OPTIONS FOR THE FORESEEABLE FUTURE

A two-year international study with natalizumab in remitting MS has been conducted over the past three years. Natalizumab is a monoclonal antibody against alpha4beta1 integrins, adhesion molecules on the surface of activated T-lymphocytes. Inhibition of these adhesion molecules stops T-lymphocytes from entering CNS tissue, thus critically reducing inflammation in the CNS and its sequelae. The ability of natalizumab to reduce the incidence of MS attacks as compared with placebo is 68%; consequently its effect compared with original drugs of first choice is doubled. Its effect of reducing objective disease activity, measurable as gadolinium-uptaking lesions on MRI, is 92% (7). Regrettably, two patients in another study assessing a combination of natalizumab with interferon beta experienced serious side effects, that is, development of progressive multifocal leukoencephalopathy (PML). PML is caused by the JC virus surviving in the renal or bone marrow of 85% of healthy individuals. In the presence of serious immunosuppression (most frequently in HIV-positive patients, those with malignancies, individuals undergoing allogenic transplantation), the virus tends to multiply and travels to the CNS, where it attacks oligodendrocytes and dissolves white matter. In most patients the disease is fatal within a couple of months. A third case of PML was identified in a natalizumab-treated patient with Crohns disease. However, this particular patient received pretreatment with infliximab (a monoclonal antibody against tumor-necrosis factor alpha, TNF alpha) and was on long-term azathioprine. It is not clear why JC virus activation, but no other opportunistic infections, occurred in the presence of natalizumab. One MS patients was immunocompromised, with melanoma in his history prior to study initiation. On 28 February 2005 natalizumab administration was discontinued worldwide, although the drug was approved by the U.S. Food and Drug Administration (FDA) for the management of MS as early as November 2004. All patients receiving natalizumab underwent a series of safety precautions to rule out additional cases and to specify the circumstances instrumental for JC virus activation. Still, it is hoped that the drug will continue to be used in monotherapy in the foreseeable future.

Other biological agents are currently undergoing clinical trials. These include monoclonal antibody against interleukin-12 (8), one of the main pro-inflammatory cytokines, and antibody against the chemokine receptor CCR2, which should block inflammatory cells from entering the CNS.

Other tested drugs are oral immunosuppressants such as fumarate (used in Germany to treat psoriasis), laquinimod (whose molecule was derived from that of linomide, successful in clinical trials in the 1990s but discontinued because of cardiotoxic effects) and cladribine (effective in MS when administered parenterally in several studies, with anticipated reduced side effects at lower doses).

A breakthrough mode of action is DNA vaccination allowing inducing tolerance to myelin autoantigens (9). This treatment is being prepared for a Phase II clinical trial.

IMMUNOABLATION WITH SUPPORT TO AUTOLOGOUS STEM HEMATOPOIETIC CELLS, CURRENT STATUS IN THE CZECH REPUBLIC

The number of patients who had undergone this experimental type of therapy for MS and entered the European registry kept in Basel, Switzerland, is over 180. Consequently, it is possible to identify some predictors associated with the highest efficacy of this therapeutic option, anticipating resumed ontogenesis of the immune system induced by different stimuli. Results available from the registry indicate the most effective treatment of MS is of 5 years duration, in patients with preserved ability to walk at least 100 m with support, and with documented high inflammatory activity of the disease (characterized by attacks of clinical exacerbation or gadolinium-enhancing lesions on MRI scans). As regards the therapeutic regimen itself, a use of unpurified grafts has proved to be most successful, although in theory such a technique results in the return of potential autoaggressive lymphocytes to the body. An unpurified graft is thus not only associated with a lower incidence of side effects of this toxic therapy but is also apparently associated with return of regulatory T-lymphocytes, which are helpful in proper development of the immune system. Progression-free interval in patients receiving this treatment is unexpectedly 6.7 years in 61% of patients (it should be noticed we are dealing with a malignant course of the disease, where spontaneous activity cessation has not been reported). Some patients show improvement of their current neurological finding. Experimental studies has furnished evidence that stem hematopoietic cells are capable of de-differentiating into cells so much pluripotent that they may give rise to new glial cells and neurons. This has been documented in the brains of patients undergoing bone marrow transplantation because of a malignancy (10).

CONCLUSION

Multiple sclerosis is no longer an intractable disease that cannot be treated. Delay of otherwise irreversible disability can be particularly expected in cases whereby immunomodulatory treatment has been initiated in the early stage of the disease. We hope research in

the near future will provide us with novel drugs not only for immunomodulation but, also, for neuroprotection.

Abbreviations:

CCR2 - chemokine receptor
CNS - central nervous system
DNA - deoxyribonucleic acid
FDA - Food and Drug Administration (U. S.)
HIV - human deficiency virus
JC virus - DNA polioma virus, JC are initials of the first diagnosed patient
MRI - magnetic resonance imaging
MS - multiple sclerosis
PML - progressive multifocal leukoencephalopathy

REFERENCES

1. **Trapp, B. D., Peterson, J., Ransohoff, R. M. et al.:** Axonal transsection in the lesions of multiple sclerosis. N. Engl. J. Med., 1998, 378, pp. 278-285.
2. **Richert, N. D., Ostuni, J. L., Bash, C. N. et al.:** Interferon beta-1b and intravenous methylprednisolone promote lesion recovery in multiple sclerosis. Multiple Sclerosis, 2001, 7, pp. 49-58.
3. **Zivadinov, R., Rudick, R. A., De Masi, R. et al.:** Effects of IV methylprednisolone on brain atrophy in relapsing-remitting MS. Neurology, 2001, 57(7), pp. 1239-47.
4. **Havrdová, E., Horáková, D.:** Roztroušená skleróza, Postgraduální medicína, 2004, 6, pp. 382-389.
5. **Rieckmann, P. et al.:** Multiple Sclerosis Therapy Consensus Group. Escalating immunotherapy of multiple sclerosis - new aspects and practical application. J. Neurol., 2004, 251(11), pp. 1329-1339.
6. **Fassas, A., Passweg, J. R., Anagnostopoulos, A., Kazis, A., Kozak, T., Havrdova, E. et al.:** for the Autoimmune Disease Working Party of the EBMT (European Group for Blood and Marrow Transplantation): Hematopoietic stem cell transplantation for multiple sclerosis: a retrospective study. J. Neurol., 2002, 249, pp. 1088-1097.
7. **Miller, D. H., Khan, O. A., Sheremata, W. A, et al.:** A controlled trial of natalizumab for relapsing multiple sclerosis. N. Engl. J. Med., 2003, 348, pp. 15-23.
8. **Vandenbroeck, K., Alloza, I., Gadina, M., Matthys, P.:** Inhibiting cytokines of the interleukin-12 family: recent advances and novel challenges. J. Pharm. Pharmacol., 2004, 56(2), pp. 145-160.
9. **Steinman, L.:** Immunotherapy of multiple sclerosis: the end of the beginning. Curr. Opin. Immunol., 2001, 13(5), pp. 597-600.
10. **Mezey, E., Key, S., Vogelsang, G., Szalayova, I., Lange, G. D., Crain, B.:** Transplanted bone marrow generates new neurons in human brains. Proc. Natl. Acad. Sci. USA, 2003, 100(3), pp. 1364-1369.

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