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REVIEW

DISEASE MODIFYING PHARMACOLOGICAL APPROACH OF MULTIPLE SCLEROSIS. A FOCUS ON GLATIRAMER ACETATE

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Abstract. Multiple sclerosis is a neurological disease with diverse treatment options, but one of the main tools of maintaining a relatively acceptable life quality is the pharmacological approach through disease modifying therapies. The objective of this paper is to give a brief presentation of the main feasible drug options, a higher attention being offered to glatiramer acetate.
Keywords: multiple sclerosis, disease modifying drugs, glatiramer acetate, BDNF

Introduction

Multiple sclerosis (MS) is one of the most disabilitating neurological diseases, described more than 130 years ago (Charcot, 1868)[1], affecting the patient in the most prolific period of his life. The term multiple refers to the diversity of the neurological deficits found during the course of the disease; sclerosis describes the sclerotic lesions, the characteristic plaques. Ethiology is only partially defined to this point; both the relapse reliever and disease modifying treatment is oriented against a presumably aberrant immunological response. Most of the drugs are designed to act against aggressive factors, and a few of them are enhancing the capacity to regenerate after the immune attack took place, such a treatment being glatiramer acetate.

Treatment options

The therapy of MS can be approached by several ways. On one hand, a therapy for relapses and a disease modifying maintenance treatment is needed. On the other hand, there's a necessity of a symptomatic treatment for the co-occurring disturbances: depression, fatigability, spasticity, cognitive dysfunction, incontinence and pain. Pharmacological therapy will be presented, for both relapse and disease modifying treatment; other options, like intravenous immunoglobulins or lymphoid irradiation are not included among the goals of this paper, nor the symptomatic treatment.

Relapse treatment

Mild relapses, which are not producing functional disabilities, are not requiring usually additional therapies, but the recommendations are divergent. If there are manifest neurological deficits, then high-dose glucocorticosteroid pulse-therapy is performed, 500-1000 mg/day for 3-5 days, the recommended drug being methylprednisolone. A former recommendation was adrenocorticotropic hormone (ACTH) therapy, but with lower efficacy, since it induces the production of several endogenous glucocorticosteroids, with diverse effects, which are difficult to be controlled, this therapy being virtually dropped today [2]. The exact mechanism is not totally known, but it causes a reduction of the peri-lesional edema and shows an intense immunosuppressive effect. The outcome of the treatment is a reduction of the length of the relapse, and of the rate of future relapses of optic neuritis, without an influence on disease progression. The pulse-therapy may be followed by gradually reduced oral prednisone treatment, but most of the authors are recommending a limited use of these drugs [3]. Severe relapses, characterized by para- or tetraplegias can benefit of plasmapheresis.

Disease modifying therapies

Interferons

β_{1b} interferon (IFN β_{1b}) was the first remedy used with the above-evoked intention. It is a recombinant

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interferon, obtained using modified Escherichia coli cultures. In MS the immunomodulatory effect of the interferons is validated; it seems that IFN β_{1b} are reducing the expression of interferon γ (IFN γ) and the expression of components of the class II major hystocompatibility complex (MHC II) on antigen presenting cells (APC), these being actually induced by IFN γ. T cell proliferation might be also reduced, and by this, the permeability of the blood-brain barrier (BBB) also. Chronic administration lowers the number of relapses and shows a significant, MRI-proved impact on lesion evolution also. On the other hand, it presents no influence on residual symptoms and neurological deficits. [4,5]

Interferon β_{1a} (IFN β_{1a}) is also obtained by recombinant technology, on cells of Chinese hamster ovary. IFN β_{1a} also reduces the rate of relapses, associated with a MRI-measured slowing of the evolution, [6], but also a positive effect on cognitive deficits, reducing the velocity of cortical atrophy [7].

The disease modifying effect is evident, but the side effects profile is none but benign: myelosuppression, elevated transaminases, depression, myopathy, myalgias, local inflammation, pain, rarely tachycardia, dyspnea etc. There's a relative lack of information during pregnancy, contraceptive methods are recommended, or the treatment should be stopped until delivery.

Returning on depression, this could be profound, leading potentially to suicide. This aspect requires an attentive monitorization.

Mitoxantrone

Mitoxantrone is an immunosuppressive agent, which inhibits T cell, B cell and macrophage proliferation, cellular elements involved in MS pathogenesis. It's clinical utility was proved for the secondary progressive, progressive-relapsing and relapsing-remitting forms of MS, the latter if lacked an adequate response to other treatments.

Mitoxantrone has an anthracenedione structure, which interferes with the DNA chain, showing a property to induce structural changes of the DNA, with functional loss. Such changes are represented by interruption of the chain, or of hydrogen bonds. The molecule also interferes with repair mechanisms, by blocking the topoisomerase II. Mitoxantrone has no selectivity on DNA; it also modifies the RNA [8].

Side effects profile limits the extensive use of the drug. Important ventricular dysfunction is described [9], with impact on ventricular ejection rate [10]. Leukemias were signaled also after mitoxantrone treatment: acute promyelocytic leukemia [11], acute myeloblastic leukemia [12]. Urinary retention, sexual disturbances are also related [13].

Risks can be partially limited by the proper use, and the benefits are recommending the drug as a solution in treatment-resistant cases by using mitoxantrone. [14].

Azathioprine

Azathioprine is an immunosuppressor recommended by some studies as an alternative to interferons, and used extensively in the treatment before these and glatiramer acetate became available [15].

The substance is a prodrug, being metabolized to 6-mercaptopurine and 6-thio-inosinic acid. 6-mercaptopurine interferes with the synthesis of endogen purines, and by this with the synthesis of DNA. The effect is more obvious on cells with a high turnover, as the lymphocytes involved in MS [16].

During the treatment a possible risk for secondary malignancies was identified [17], but mostly after treatment durations exceeding 10 years, or in case of high, cumulative doses [18]. Medullar suppression and liver toxicity were reported more frequently, but a close monitorization of the treatment reduces the incidence of these side effects.

The treatment provides a control of the disease comparable with the effect of beta interferons, regarding relapse frequency, being a feasible alternative mainly for patients requiring high doses of corticosteroids [19].

Methotrexat

Methotrexat induced immunsuppression can be applied also in MS. The drug competitively inhibits, with high affinity, dihydrofolate reductase (DHFR). The enzyme assures the disponibility of tetrahydrofolate, the active form of folate, a rate limiting stage of thymidine synthesis. DNA production is reduced, affecting also the lymphocytes involved in MS. It seems that the molecule limits the expression of adhesion molecules of the T cells also. [20].

Several studies were conducted to evaluate response to methotrexat, using the expanded disabilitz status score (EDSS), with favorable, but highly variable outcomes [21,22]. Recent evaluations state that there's no important effect on disease progression [23], or relapse frequency. The side effects were relatively mild, given the used dose range; tolerability was acceptable, versus placebo.

The need for further studies is suggested, to evaluate the role of the drug in MS treatment.

Cladribine

The usually administered MS therapies are sharing the parenteral route, and this could influence adherence to treatment. An emergent therapeutical option is cladribine, which besides the injectable form, used in oncology and MS, is manufactured as tablets also [24].

Cladribine is a purine analogue, which interrupts

the repair mechanisms and synthesis of DNA, by interfering with the endogenous purines [25]; it manifests both CD4 and CD8 T cell, B cell and to some extent NK cell tropism [26].

If MR criteria were evaluated, the drug presented a clear lesion modifying effect, without significant side effects after parenteral use, although these appeared after high doses, consisting mainly of myelosuppression and severe infections. The oral administration will probably not reach the toxic concentrations, and a better safety profile will be granted, but there are still questions, if effectiveness will not be affected [27].

Natalizumab

Natalizumab is a recently introduced monoclonal antibody, as a novel disease modifying treatment in MS. This is also the reason for poor experience regarding the drug, to this point. There are opinions sustaining the efficiency of the drug on both the progression and the relapses, in case of the relapsing-remitting form of MS [28]. Still, there are no convincing data for the other types of MS, and for the role of the medication in a combined therapy, yet. [29,30].

Natalizumab couples with the a4 subunits of integrins, like a4β1 or a4β7, these being expressed on the surface of T lymphocytes. Integrins are required by lymphocytes in order to bind with endothelial receptors like the vascular cell adhesion molecule (VCAM-1). This facilitates the crossing of the T cells through the BBB. If the mechanism is inhibited, then the number of lymhocytes reaching the CNS will be reduced [31].

The efficiency of the drug should be evaluated on higher number of patients, but concomitantly there are some concerns regarding the side effects, mainly the risk of developing multifocal leukoencephalopathy, and the risk of severe infections [32,33].

Until these controversies are not elucidated, the role of natalizumab in MS is difficult to appreciate.

Glatiramer acetate

To prevent the evolution of the characteristic lesions, there are repair mechanisms, induced mainly by neuronal growth factors. Their production may be influenced also by cytokines involved in inflammation. The principal neurotrophic factors NGF related neurotrophins: nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), neurotrophin-4 (NT-4); ligands of the glial cell-line neurotrophic factor family (GFL): glial cell-line neurotrophic factor (GDNF), neurturine, artemine, persephine; neuropoetic cytokines: ciliary neurotrophic factor (CNTF), leukemia inhibitory factor (LIF) and others with neurotrophic effect: insulin-like growth factor 1 (IGF-1), neuregulin glial growth factor (GGF-2), etc. Their role is not limited to the formation of the central nervous system (CNS), these factors are acting on mature neuronal tissue also, inducing and sustaining repairs and plasticity. Among the demyelinating disease, the role of these factors is not entirely elucidated, but it seems that BDNF and NT-3 may facilitate long spinal pathway regeneration, and NGF stimulates olygodendrocytes. Their level in the CNS is high at the debute of these diseases, possibly reducing the effects of the immune attack or stimulating protective factors, represented by several functions of the olygodendrocytes [34].

An induced inflammatory reaction among laboratory animals, with resemblance to MS is the experimental autoimmune encephalomyelitis (EAE) [35]. This is obtained by active immunization with the myelin basic protein (MBP). It was observed although that if animals with previous neuronal damage are immunized, then it seems that a protective effect is validated. The dual character of the immunization constitute the basis of some neuroprotective therapies in MS, explained through the expression of epitopes by the damaged cells, these being targets for the immunized cells [36].

Several factors are considered to have neurotoxic effects: Th1 specific cytokines, chemokines, leukotrienes, matrix metalloproteinases (MMP), nitric oxide (NO), glutamic acid (Glu), reactive species of oxygen etc. These are balanced by neuroprotective factors: Th2 cytokines, BDNF, NGF, transforming growth factor (TGF), tumor necrosis factor (TNF) etc. BDNF and it's receptor, the tyrosine kinase B (TrkB) are intensely expressed around the demyelinizated lesions, BDNF by the astrocytes, neurons and mostly by the recruited inflammatory cells, and TrkB by astrocytes and neurons. [37].

Even if these genes are expressed predominantly in the CNS, their products were isolated also on cells from peripheral blood. These observations led to the use of neurotrophic agents in the treatment of MS; even if their expression offers a protective effect, it is postulated that the local expression is insufficient to prevent tissue damage. Still, retroviral transfection of the zone with the BDNF gene or the isoimmunization is risky, due to the possibility of induction of an EAE related syndrome.

In order to increase local BDNF levels, the most realistic approach is by using glatiramer acetate. The drug is a standardized acetated mixture of four amino acids: L-alanine (L-Ala), L-glutamine (L-Glu), L-lysine (L-Lys) and L-tyrosine (L-Tyr), formerly known as copolymer I [38], which was designed to present structural resemblance with MBP, to see if it could induce EAE in animals. The mixture failed to produce the syndrome, but presented a protective effect in animals already having EAE.

The mechanism of action of glatiramer acetate was unknown until recently, when several studies partially revealed an important role mainly on cell-mediated immunity. The major effects of the drug are: in vitro T cell proliferation, polyclonal proliferation of lymphocytes in the peripheral blood, binding with MHC I and II, reduction of T cell migration, Th1 to Th2 switch among the peripheral lymphocytes [39] – increased IL-10 and $_{m}$RNA for TGF-b and interleukine 4 (IL-4) and reduction of $_{m}$RNA for TNF-a, Th1 to Th2 switch of GA specific T cells, crossed inhibition/stimulation of MBP-specific T cells, T cell receptor (TCR) antagonization, anergy induction in MBP-specific T cells, production of non-neutralizing GA-specific antibodies, stimulation of GA-specific T-CD8 cells, effects on APCs etc. Its multiple effects are insufficiently known and understood, but it seems that these are converging towards the production of neurotrofic factors, predominantly BDNF [40].

BDNF, as presented above, has a protective effect in MBP induced EAE on laboratory animals, and, as a consequence, a possible clinical impact on MS. [41].

The recommendations for using the drug in MS came from preclinical studies. The main expectations were the potential reduction of relapses and a positive influence on the functional deficits. Early treatment in clinically isolated syndrome delays further relapses, by this also the diagnosis of MS [42].

Recent studies, using the EDSS score as an evaluation method, are suggesting that even if the mechanism seemingly affects the pathogenesis, glatiramer acetate shows no effect on primary and secondary progression of MS [43]. Still, the relapsing form shows benefits by reduction of relapse rate, and reduction of the risk for further relapses [44].

The long-term treatment is well tolerated, few side effects are validated, and these are usually mild – flushing, palpitation, sweating, dyspnea and anxiety [45]. Sometimes injection related complications occur, like paniculitis [46], lipoatrophy [47].

Conclusions

The main disease modifying drugs are further on interferons and to a lesser extent to this point, glatiramer acetate, in progressive forms of MS, although the latter has a more promising profile, and a more specific mechanism than interferons. Even if controversies are still present regarding progression, the safety profile acts as a balancing factor, at least in the relapsing form. Further investigations may prove a more important role of Glatiramer acetate in the treatment of the disease. Immunosuppressors represent a valid option, but the side effects limit their use. Novel, emerging, disease modifying drugs are lacking enough information regarding their long-term clinical effectiveness.

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