



Treatments of Multiple Sclerosis

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ABSTRACT

Multiple sclerosis is an auto immune demyelinating and debilitating disease. It affects many people in the world and is the main cause of chronic neurological handicap in young adults. The first treatments were based on the immunosuppressives which have been replaced during the last years by biotherapies injectables initially and recently oral forms emerged providing prescribers and patients multiple choices according to the cases.

Keywords: Multiple sclerosis; Immunosuppressives; Biotherapies; Oral forms

INTRODUCTION

Multiple sclerosis is the most common autoimmune disease of inflammatory demyelinating central nervous system (prevalence of 1/1000) [1]. On multifactorial origin, it is the leading cause of chronic neurological disability among young adults [1-2]. The first treatments showed variable effectiveness associated with a number of side effects that have been changed in recent years by the biopharmaceuticals and have shown better efficiency and changed the disease's prognosis [3].

Multiple Sclerosis (Ms)

Multiple sclerosis is a multifactorial disabling disease. Its risk factors include immunological, genetic and environmental causes (class II alleles of the main histocompatibility complex HLA-DRB111 locus, as well as ILR2 and ILR7 genes) [2]. Diagnosis is mainly clinical, it affects young adults. During the disease, the central nervous system is the area of multifocal sclerosis demyelination accompanied by loss of oligodendrocytes and astroglial cicatrization. The axonal affection is also noticed earlier, as well as the inflammatory process [2]. It evolves in four models [2]:

The Relapsing remitting:

It concerns 85 to 90% of the cases of multiple sclerosis at the beginning and is characterized by relapses separated by periods of remission, complete or with sequelae and residual deficits.

The Secondary progressive:

The Secondary progressive is preceded by the relapsing-remitting form.

The Primary progressive:

It concerns 10 to 15% of early multiple sclerosis patients and is characterized by a continuous progression from the beginning with a few periods of stability.

The Progressive relapsing:

The Progressive relapsing is characterized by a progression from the beginning associated with acute relapses with or without recovery.

Multiple Sclerosis pharmacological treatment's history

In the 1970s, multiple sclerosis treatment used immunosuppressives based mainly on Azathioprine, Methotrexate and Cyclophosphamide. However, these molecules were known for their variable clinical efficacy between individuals and almost many constant side effects, potentially serious side effects and potentially serious. Therefore, their long-term prescription remained delicate and required close medical supervision [3]. The early 1990s appeared new drugs, biotherapies such as: subcutaneous Interferon Beta-1b (1995) and intramuscular Interferon Beta-1a, subcutaneous Interferon Beta-1a and Glatiramer Acetate, characterized by an immune modulating effect. They are more effective than immunosuppressives, decreasing by 30% inflammatory episodes frequency and intensity [1-3]. Several studies have been published comparing these molecules, the Danish study (SC Interferon Beta-1a versus SC Interferon-Beta 1b), EVIDENCE study (SC Interferon Beta-1a versus IM Interferon Beta-1a), INCOMIN study (SC Interferon-Beta 1b versus IM Interferon Beta-1a), BECOME and BEYOND studies (SC Interferon-Beta 1b versus Glatiramer Acetate) and REGARD study (SC Interferon Béta-1a versus Glatiramer Acetate), highlighting moderate efficacy superior to Interferon-Beta administered subcutaneously several times a week compared to Interferon Beta administered intramuscularly once a week, equivalent efficacy between the two Interferon-Beta preparations administered by subcutaneously and equivalent efficacy between Interferon Beta administered subcutaneously and Glatiramer Acetate [4]. This first treatment line was enhanced by a second line of arsenal, including Mitoxantrone (in 2003) have received a marketing authorization for aggressive relapsing forms of multiple sclerosis, and Natalizumab (in 2007) the first monoclonal antibody that received marketing authorization for MS active forms of [1]. Since 2010, some oral forms appeared (Fingolimod, Teriflunomide, Dimethylfumarate Fumaric Acid Esters (DMF), Laquinimod), with innovative pharmacological modes of action [3] as well as many "zumab" aiming aggressive forms (Alemtuzumab, Daclizumab, Rituximab...) [1].

Treatment targets mechanisms

For early demyelinating phase in remittent-recurrent forms secondary progressive, there is an inflammatory process associated with a permeability of the blood brain barrier. Lesions histopathological exam on biopsy or autopsy revealed the presence of inflammatory T cells, B cells and macrophages. Immune activation via the helper T1, underlined by interleukin 2 (IL2) expression, among others, is one of multiple sclerosis lesions characteristics. CD8 + lymphocytes exert neurotoxic effects on axons. Moreover, various mechanisms involvement is confirmed by a decrease in multiple sclerosis activity in patients treated with immunomodulators reducing the immune response mediated by Th1 (Interferon Beta), increasing Th2 and Th3 (Glatiramer Acetate) response or block movement of blood T cells to the central nervous system (Natalizumab). Finally, experimental allergic encephalomyelitis (EAE), an animal model of MS, can be induced by myelin antigens including myelin oligodendrocyte glycoprotein (MOG) [5].

MULTIPLE SCLEROSIS MANAGEMENT**The objectives and benefits of treatment****Reduce relapses frequency:**

This reduction is the primary criteria for multiple sclerosis treatments evaluation. The clinical and radiological remission is the aim in specific case of active forms accumulating throughout severe or frequent relapses of short-term disability. Thus, for these patients, it is appropriate to suggest immediately second-line treatment or in case of first-line treatments failure [1].

Avoid long-term disability onset:

The main of multiple sclerosis problem is the risk of motor impairment onset, cognitive, sphincter, and social. It most often appears slowly, with a median onset limiting 500 meters of eight years, to have to use a cane to travel 100 meters in 20 years, and appeals to a wheelchair in 30 years, hence the importance of diagnosis and early treatment [1].

Progressive forms treatment:

Multiple sclerosis progressive forms of whether they are immediately progressive or secondary progressive (progressive passage after remitting phase) different from relapsing forms by more quick progression of disability,

because of massive neuronal loss related with a cerebral and meningeal inflammation diffuse seeming independent of peripheral inflammation. For this, treatment's target in progressive forms must be different from that of relapsing forms: remyelination strategy, neuroprotection, action on microglial cells, treatment passing the blood brain barrier [1-6].

Acute relapses management

Relapses corresponding to periods of acute inflammation, treatment are based partly on rest, on the otherhand on anti-inflammatory drugs, particularly steroids at high doses intravenously (IV). Thus, methylprednisolone is used as a bolus at a dose of 1000 mg / day from 3 to 5 days [5]. Recently, COPOUSEP study showed that 1000 mg of methylprednisolone / day for 3 days, administered orally, were not inferior in terms of clinical recovery and tolerance to their intravenous administration, taking account the expected benefits of the procedure (less invasive, no hospitalization, early access to treatment ...). Moreover, the indication of high dose corticosteroids should be put by a neurologist after he validated the relapse, validated the need to treat and organized the pre-therapeutic assessment. In 2016, the multiple sclerosis relapses can be treated in outpatient by oral methylprednisolone 1000mg/day for 3 days, on hospital prescription. The procedure must be secured by good coordination between the neurologist and the patient. However, the prescription of low dose oral corticosteroids is not recommended in multiple sclerosis [7].

Background treatment

The treatments used are meant to induce a depletion of cells bearing CD20 antigens, CD52 or CD4, inhibition of cytokines such as interleukin 2 (IL2), CD25, TCR (T cell receptor), to reduce extravasation at the level of blood brain barrier or regenerate myelin [5]. These treatments are mainly recommended in remittent-recurrent forms, with modest efficacy evaluated by the existence of patients responders or not.

Immunomodulators

Represented by Interferons Beta (INFB -1a, INFB-1b) and Glatiramer Acetate, are the first treatments on the field. Interferons inhibit Th1 cytokines, activate cytokines Th2 secretion and reduce auto-reactive cells passage across the blood brain barrier. The Glatiramer Acetate, meanwhile, causes cross-reaction with the basic protein of myelin and causes induction of suppressor T cell antigen-specific, which secrete anti-inflammatory cytokines [1]._During treatment, a variable percentage of patients developing anti-interferon neutralizing antibodies that seems to cancel their clinical efficacy. Anti-Glatiramer antibodies have also been highlighted in most of patients, without neutralizing the clinical effect [1-5].

Immunosuppressives

Their use in multiple sclerosis is based on pathophysiological arguments rather than on clinical efficacy evidence. They are only considered in case of aggressive relapsing MS or progressive MS (either primary progressive or secondary progressive):

Mitoxantrone: It has a similar structure to anthracyclines, it is an anthracenediones derivative developed and used in oncology as a cytotoxic agent intercalating DNA and acts on the ARN synthesis and inhibits topoisomerase II. It also inhibits inflammatory cytokines secretion such as interferon gamma, TNF (tumor necrosis factor) and interleukine-2(IL-2). It is mainly reserved for aggressive forms with sequelae or in case of significant disability worsening in twelve months, and contrast enhancement on magnetic resonance imaging (MRI). Its use is very limited. This molecule has cardiac risk [1-5].

Cyclophosphamide: It is an alkylating agent used in cancer for its antimetabolic properties and in several autoimmune diseases treatment as non-specific immunosuppressive acting on the B and T lymphocytes functions. Its use in MS is based on its ability to reduce the pro-inflammatory response type Th1 for Th2 / Th3 response [1].

Monoclonal antibodies

Natalizumab: Is a humanized monoclonal antibody (IgG4) directed against alpha 4 integrin expressed on the surface of leukocytes whose activation allows its interaction with the cellular adhesion molecule VCAM-1, main step in the leukocyte passage through the vascular endothelium and the passage of the blood brain barrier. Natalizumab preventing activated lymphocytes adhesion to vascular endothelium decreases parenchymal inflammation.

Indeed indicated as second-line for patients with active form of MS who have not responded to a full and adequate course of IFN beta or even first-line for patients with severe RR MS and quick evolution [1-5-8]. However, rare cases of progressive multifocal leucoencephalopathy have been noticed, their frequency is estimated at less than 1/1 000 patients treated, requiring an evaluation of benefit risk of Natalizumab in each treated patient, performing meticulous pretreatment assessment, limiting its administration to very active MS, with strict monitoring, clinical and by magnetic resonance imaging (MRI) [5].

Alemtuzumab: It is a humanized monoclonal antibody (IgG1), already indicated in chronic lymphocytic leukemia. It is directed against the CD52 antigen present on the surface of most lymphocytes and monocytes. It induces lysis mediated by the complement system [7]. The binding of this antibody with CD52 on the surface of leukocytes is cause their elimination by complement activation and antibody dependent cellular cytotoxicity. Lymphocyte reconstitution is variable and takes on average 6 months for LB and more than a year for LT. One of the major side effects associated with Alemtuzumab and limiting its prescription is the risk of autoimmunity estimated at 30% for thyroid impairment and 3% for idiopathic thrombocytopenic purpura for 5 years. The development of these autoimmune diseases is probably related to lymphocytic immune reconstitution B and T [8].

Daclizumab: Is a humanized monoclonal antibody (IgG1) against the alpha receptor IL2 cytokine involved in the activation of T cells [10]. The prime mover of the development of this molecule was to block the proliferation of activated LT by inhibiting the signaling pathway of IL-2. In practice, its primary mode of action appears to go through an increase in the frequency of cells CD56 + Natural Killer regulators. The safety data available in the recently published phase III study reported more risk of infections, skin rashes and liver problems than with the Interferon Beta -1a [8].

Rituximab: This is a chimeric monoclonal antibody (IgG1), responsible for lymphocytes B CD20+ depletion [11]. The binding of these antibodies to LB causes their elimination (by complement activation and cellular cytotoxicity depending on antibodies) persistent 6 to 8 months. This is probably the loss of cell functions LB (antigen presentation, cytokine secretion) that mainly the efficacy of anti-CD20 antibody. Severe infections were reported in patients with lymphoma, lupus or rheumatoid arthritis treated with Rituximab. Cases of progressive multiple leucoencephalopathy (over 150 cases) have been described in this therapy but in immunocompromised patients receiving multiple immunosuppressive agents. However, in multiple sclerosis patients, in whom such antibodies are used as monotherapy, no cases of progressive multiple leucoencephalopathy have been reported to date [8].

The oral forms

Fingolimod: Is the first oral form drug available. It is prescribed for second intention. It acts as an agonist of receptors of sphingosine-1-phosphate, it maintains the T and B lymphocytes in secondary lymphoid tissues, thereby preventing their migration into the central nervous system and causing a reversible lymphopenia two months after stopping treatment. Fingolimod shows out superiority to other biotherapy, on reducing the number of relapses and the number and activity of lesions detected by magnetic resonance imaging (MRI). Cardiac monitoring is necessary during the first dose administration [3-12].

Teriflunomide: It is a pyrimidine synthesis inhibitor, it inhibits selectively and reversibly dihydroorotate dehydrogenase, a mitochondrial enzyme necessary for pyrimidine synthesis. It thus reduces cells proliferation that needs pyrimidine de novo synthesis to occur (activated lymphocytes) [3-13]. Other complementary mechanisms of action have been reported as blocking specific cytokine signaling, or the inhibition of COX-2 [8].

Dimethyl fumarate: It is a fumaric acid derivative, already used in psoriasis. Preclinical studies showed an antioxidant effect through the activation of the transcriptional direction of nuclear factor NRF2 and increased expression of NRF2-dependent antioxidant genes [3]. The safety data from the clinical phase III trials and post hoc analyzes related phenomena flushing, gastrointestinal disorders, lymphopenia (4-5%) and elevated liver enzymes. Although no opportunistic infections has been reported in the Phase III trials, three cases of progressive multiple leucoencephalopathy have been reported (at 23/10/2015) at patients treated in monotherapy by DMF (not previously having received treatments for progressive multiple leucoencephalopathy risk) for multiple sclerosis or psoriasis. The risk of progressive multiple leucoencephalopathy in DMF seem strongly linked with a fairly deep and prolonged lymphopenia <500 / mm. The EMA (European Medicines Agency) has since issued quarterly monitoring recommendations of the blood counts formula and stop in case of treating lymphopenia grade 3 than 6 months [8].

Laquinimod: Is a molecule having anti-inflammatory and neuroprotective properties. The first results of a phase III study showed that the drug was able to slow down the neurological disability progression and brain atrophy, but decrease only slightly annual relapses risk [3- 14].

CONCLUSION

Since the nineties, when the first commercialization of a Interferon Beta, multiple sclerosis therapeutic arsenal continues to develop. Several studies are held to understand the physiopathological mechanisms underlying the disease's progression. Similarly, many molecules are being developed in hopes to find active molecules on progressive forms that are the most disabling forms of the disease.

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