

NEWS IN MULTIPLE SCLEROSIS TREATMENT

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Abstract: The therapeutic arsenal in Multiple Sclerosis (MS) has developed after the 90's by using beta-interferon, glatiramer acetate, and then natalizumab. Currently, five oral therapies are in phase III studies or have recently been approved for the treatment of relapsing-remitting MS: cladribine (approved in Russia and Australia), fingolimod (approved in the US and Russia), BG-12 (phase III), laquinimod (phase III) and teriflunomide (phase III). The new monoclonal antibodies shall inaugurate the second generation after natalizumab.

Rezumat: Arsenalul terapeutic în Scleroza Multiplă (SM) s-a dezvoltat după anii 1990 cu utilizarea interferonului beta și a glatiramer acetatului, apoi natalizumab. În prezent, cinci terapii orale sunt în studii de fază III sau au fost recent aprobate pentru tratamentul SM recurent-remisiv: cladribina (aprobată în Rusia și Australia), fingolimod (aprobat în Statele Unite și Rusia), BG-12 (fază III), laquinimod (fază III) și teriflunomida (fază III). Noii anticorpi monoclonali vor inaugura a doua generație după natalizumab.

SCIENTIFIC ARTICLE OF BIBLIOGRAPHIC SYNTHESIS

Multiple Sclerosis (MS) begins with the activation of T-lymphocytes confronted with one or more antigens of yet unknown origins. Once activated these lymphocytes adhere to the vascular endothelium and penetrate the central nervous system (CNS) where they attack the myelin sheath of the neurons. These autoreactive T-lymphocytes are divided into 2 groups: Th1 lymphocytes which produce pro-inflammatory cytokines (IFN γ , TNF α , IL 1,2 and 12), and Th2 lymphocytes which produce anti-inflammatory cytokines.

The anti-inflammatory response causes the metalloproteinases, enzymes which determine the permeability of the blood-brain barrier, facilitating the infiltration of new T lymphocytes. The pro-inflammatory cytokines are mostly responsible for the progressive demyelination of the neurons. They activate cells (macrophages, lymphocytes) which in their turn produce antibodies, nitric oxide (NO), and other cytokines toxic for the oligodendrocytes (thus for the myelin) (1).

If, for a long period of time, the only treatment for this disorder was to administer immunosuppressors which bear a reduced efficacy and a considerable toxicity, the marketing of the beta-interferon, of the glatiramer (Copaxone), and then of the monoclonal antibodies, natalizumab (Tysabri), represented a major progress in the treatment of the disorder. These therapeutic strategies which are blocking or slowing down the process of demyelination, represent options accessible to MS patients according to the protocols. They act upon the two intricate components of this disorder: demyelination and inflammation.

For a long time the immunosuppressors have constituted the basic treatment for the severe and progressive forms of MS. Mitoxantrone, an immunomodulating

antineoplastic used for the treatment of breast cancer, is moderately used in the MS treatment, due to its cardiotoxicity and haematotoxicity. Other immunosuppressors: cyclophosphamide, methotrexate, azathioprine, cyclosporine, have a non-specific anti-inflammatory and/or immunosuppressive action in MS; their indication is reduced.

Beta-interferon (IFN-beta) is active in relapsing MS and on the evolution of the MRI lesions. The efficacy of this interferon regarding the severity of the long-term achieved disability remains less obvious and does not prevent the disorder to evolve towards secondary progressive MS. IFN is not being indicated in primary progressive MS. The tolerance to IFN treatment remains medium: injection-site reactions, flu-like syndrome frequently appearing at the beginning of the treatment, depression, alopecia, etc.

The glatiramer acetate (Copaxone) is an immunomodulator developed because of its efficacy in preventing and controlling the gravity of the neurological disorders observed in experimental autoimmune encephalomyelitis animals. Administered to human patients, it considerably reduces the number of relapses for a prolonged period of time.

The glatiramer action mechanism is not very well known. It places itself on the histocompatibility antigens expressed by the peripheral macrophages, and thus facilitates differentiation of anti-inflammatory specific T suppressor lymphocytes. These lymphocytes cross over the blood-brain barrier, then they are reactivated in the CNS where they determine the production of anti-inflammatory cytokines and reduce the production of pro-inflammatory cytokines.

The glatiramer treatment is recommended in patients intolerant of IFN-beta or for those presenting uncontrolled epilepsy, hypersensitivity. Regard and Beyond studies have

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shown that it presents a therapeutic activity similar to IFN regarding the risk and the time interval until a new relapse. This drug offers a satisfactory tolerability. The transitory side effects may appear after injection: chest pain, dyspnea, palpitations, tachycardia. Local effects have also been noted: erythema, pain, pruritus, edema, inflammation, induration. On the long term one can note arthralgia, peripheral edema, tremor, asthenia, lymphadenopathy (2).

Natalizumab is an IgG4 immunoglobulin specifically directed against 2 human integrins very well expressed on the leukocytes surface. It inhibits transmigration of mononuclear leukocytes across the endothelium into inflamed parenchymal tissue and especially the passage of the activated T-lymphocytes through the blood-brain barrier, at the origin of the central inflammatory relapses. Natalizumab is recommended, in intravenous infusions 300 mg every four weeks, as monotherapy for the treatment of patients with highly active relapsing remitting MS despite the administration of IFN-beta, or in patients presenting severe relapsing-remitting MS with fast evolution.

Natalizumab has a positive effect on the inflammatory activity revealed by MRI, on the relapses rate, and reduces the progression of disability after two years of treatment. The efficacy appears to be higher than in the case of interferon or glatiramer therapy: its using in monotherapy causes a 68% decrease in annualized relapse rate and a 42% and 54% decrease in the progression of the disease (after 12 and 24 weeks) versus placebo. The safety profile of this drug explains its limited recommendation level for a particular group of patients. Most of those treated present at least one of the following side-effects: headache, asthenia, rhino-pharyngites. There also appears the risk of liver toxicity thus a check-up of the liver function is recommended for the treated patients. Exceptionally, death may occur as a result of a progressive multifocal leukoencephalopathy (PML). 75 cases of PML were recorded in November 2010 all over the world, in cases of natalizumab administration (3,17).

MS treatment benefits or may benefit from the administration of old drugs whose interest in neurology is worth being proved.

Cladribine, used of the intravenous form in leukemia treatment, has an immunomodulatory action especially directed against the CD4+ and CD8+ T lymphocytes: its active metabolite is responsible for inhibiting the DNA synthesis and its redressing, leading to apoptosis. Administered orally in patients with MS, cladribine crosses the blood-brain barrier in order to act directly into the central nervous system. A phase III study (CLARITY) in relapsing-remitting MS included 1300 patients (with ≤ 5.5 EDSS score) who presented at least one relapse within the last 12 months. These patients have been randomized to receive either 3.5 mg/kg or 5 mg/kg cladribine, or placebo administered in four cycles of 5 days treatment within the first year and two cycles the next years. Patients treated with cladribine have presented a significantly decrease in annualized relapse rate compared to the placebo (reduction of 57.6% and 54.5% for the 3.5mg/kg and the 5 mg/kg respectively). At the same time the study of MRI activity has confirmed the interest of cladribine versus placebo. Among side-effects, one should note anemia, lymphocytopenia and neutropenia, increased risk of infection (20% of the patients have presented signs of herpes reactivation; one female patient has presented a tuberculosis reactivation). Five cases of cancer (melanoma, pancreatic adenocarcinoma, ovarian cancer, ORL cancer and choriocarcinoma) have been detected without any proven connection to cladribine. The patients who have finished the two years of treatment as part of this study have were included into

an extension of the study in case with the purpose of providing information regarding the safety, the tolerability and the clinical long-term benefit of the treatment.

At the beginning of 2011 Merk (pharmaceutical company) will market cladribine (Movectro) in Russia and Australia. The drug will be available in oral tablets and it is recommended in relapsing-remitting MS patients (4,17).

Minocycline is a tetracycline with anti-inflammatory properties: it prevents lymphocytes to cross the blood-brain barrier. Administered in some MS patients, it determines a reduction of the active lesions on MRI. This information still needs to be checked in large groups of patients (5).

Mycophenolate is used to prevent the rejection of the allograft on transplant patients. Recently, it has been recommended in more neurological disorders treatment, among which primary progressive MS or secondary progressive MS. Administered in 45 patients for a period of 3 years, either as monotherapy, or with the purpose of sustaining a prior mitoxantrone treatment, it reduced the frequency of the relapses and stabilized the disability. The side-effects were: infections and gastrointestinal disorders (6).

Various studies suggest that statins bear neuroprotective properties, which still remain to be demonstrated. A double blind, randomized controlled study versus placebo has been evaluating the safety, tolerability and efficacy of the pravastatin (40 mg/day). Its results show a good tolerability and a favorable effect on the inflammatory parameters analyzed on MRI. The association of atorvastatin (20 mg/day) with IFN-beta revealed itself as efficient and well-tolerated in MS, over an 18-month period. A randomized phase II study versus placebo (MS-STAT) with simvastatin (80 mg/day) in secondary progressive MS analyzes the capacity of simvastatin to reduce the degree of cerebral atrophy: the results will be published in 2011 (7,16).

A study regarding the prevention of bone lesions by administrating vitamin D3 and calcium in MS, suggests a potential benefit due to the intrinsic immunomodulatory properties. High dose levels (> 10000 units/day) determine clinical improvement with a good tolerability. However, contemporary data does not allow us to declare that vitamin D3 can change the evolution of MS (8).

The old immunomodulatory treatments proposed in MS therapy present only a partial efficacy regarding the frequency of relapses. However, a number of studies underline the growing importance of the new immunomodulators: fingolimod, teriflunomide, fumarate, etc.

Fingolimod (FTY 720) has an original action mode: it is a modulator of the sphingosine 1-phosphate. Preventing the egress of lymphocytes from lymph nodes, it determines the reduction of potentially auto-aggressive lymphocytes infiltration into the CNS. Thus, preventing the passing of the lymphocytes into the blood, fingolimod causes lymphopenia. Its efficacy is explained partly by the fact that it affects not only the T and B lymphocytes, but also the macrophages, thus reducing the toxic action of the cells responsible for the cerebral lesions. This treatment can be administered orally. The results of the phase III FREEDOMS (versus placebo) and TRANSFORMS (versus interferon) studies lead to market this molecule in relapsing-remitting MS: they confirm the conclusions of the phase II studies and their extension to a period of 5 years.

The double-blind, randomized FREEDOMS study versus placebo, over a 2-year period, included 1272 patients with relapsing-remitting MS, 18 to 55 years of age and EDSS score ≤ 5.5 . The patients included must have presented at least one relapse during the last year or at least two relapses during the last two years. Two doses of fingolimod have been tested:

0.5 and 1.25 mg/day. The patients involved into the FREEDOMS study have been assessed clinically (EDSS scale) and MRI (every 3 months), but also participated to a functional clinical assessment (Multiple Sclerosis Functional Composite: the assessment of hand dexterity, of walking speed, and cognitive assessment by PASAT scale). 81% of the patients have finished the study in time. Fingolimod turned to be superior to placebo regarding the annualized relapse rate (0.18 for 0.5 mg of fingolimod, 0.16 for 1.25 mg of fingolimod, 0.40 for placebo), the risk of disability progression over a 24-month period and the MRI abnormalities.

The TRANSFORMS study included 1292 patients divided into 3 groups (fingolimod 0.5 mg/day, 1.25 mg/day and intramuscular IFN-beta 1a, 30 µg/week). The main assessment criterion was the annual relapse rate and the two secondary endpoints were the number of new hyperintense lesions on T2-weighted MRI at 12 months and progression of disability that was sustained for at least 3 months. For the 1153 (89%) patients completed the study, the annualized relapse rate was lower in both groups receiving fingolimod (0.20 in the 1.25-mg fingolimod group and 0.16 in the 0.5-mg fingolimod group; 0.33 in the interferon group), representing a reduction of approximately 38% and 52% compared to IFN for the 1.25 mg and 0.5 mg doses. To the same extent, the percentage of patients who did not present relapses by the end of the study was significantly bigger in the fingolimod group than in the IFN group (79.8% for fingolimod 1.25 mg/day; 82.6% for fingolimod 0.5 mg/day and 69.3% for IFN-beta). The risk of disability progression was not different between the groups, but the study did not last but for 12 months.

As for the radiological secondary endpoints, the clinical results were corroborated with a significant reduction in the appearance of new T2 lesions in the fingolimod group versus the IFN group.

As in the case of all immunosuppressors, the aspect of the long-term tolerance arises. A first unexpected side-effect is reversible posterior leukoencephalopathy. Fingolimod can also cause bradycardia, heart rate disorders, hypertension (especially with high dosage), increased transaminases values, and an immunosuppression with the activation of latent viral infections (herpes simplex, varicella-zoster) and upper airway infections. Fingolimod is the first oral treatment that has been proven to be efficient on the clinical parameters as well as on the radiological one, compared to a reference treatment in relapsing-remitting MS.

The pharmaceutical company Novartis will market fingolimod (Gylenia) as oral tablets. The medication was approved in Russia and the United States and it is recommended in patients with relapsing-remitting MS (9,10,17).

Laquinimod belongs to the linomide family: its action mechanism on the immune system is not completely clarified. A phase II study compared the effects of two doses of laquinimod (0.3 and 0.1 mg/day) versus placebo in 200 patients. With the 0.3 mg/day dose the active lesions have been reduced by 44% after a period of 6 months, especially as the patients initially presented a high number of active lesions. The tolerability is good, but the study was realized with relatively small doses, theoretically risk-free, and for a short period of time. Laquinimod seems less efficacy on MRI active lesions (52%) compared with IFN-beta (80-90%). Two phase III studies are in progress. The ALLEGRO study has enrolled 1000 patients with relapsing-remitting MS treated with laquinimod (oral dose of 0.6 mg/day) or placebo. The BRAVO study has enrolled 1200 patients with relapsing-remitting MS treated with laquinimod (oral dose of 0.6 mg/day), placebo or Avonex. The results of these studies are expected in 2011 (11).

Teriflunomide, an immunosuppressor used in rheumatoid arthritis treatment, has been evaluated in a phase III study (TEMPO) in 1088 patients with relapsing-remitting MS, divided into three groups: placebo, teriflunomide 7 mg/day, and teriflunomide 14 mg/day oral dose. This 2-year study presents a significant reduction of MRI active lesions, including the total lesion volume, by 39%. A reduction in the annualized relapse rate by 31% compared to placebo also appears obvious, as well as a reduction of disability progression by 30% (for the 14 mg dose). Among the side-effects one should note respiratory infections (pharyngitis, pneumonia), hepatic cytolysis (11).

Dimethyl fumarate (BG-12) offers an interesting perspective regarding MS therapy. It has an anti-inflammatory effect and probably a neuroprotective one. Its action mechanism is unknown: the depletion of tissues in glutathione, the alteration of cytokines secretion, pro-apoptotic action.

A study including 257 patients has been comparing for 6 months the efficacy and tolerability of dimethyl fumarate versus placebo in relapsing-remitting MS. 240 mg three-times-daily dose dimethyl fumarate reduced the number of the lesions revealed by brain MRI. The side-effects were mainly gastrointestinal events and hot flush; contrary to what other studies revealed, clinically significant anaemia or neutropenia do not appear.

This phase II study compared three oral doses of fumarate versus placebo in these relapsing-remitting MS patients. The primary endpoint was the number of new lesions on MRI scans at weeks 24, and 48. Compared to placebo, only the patients who received the biggest dose of fumarate presented a significantly smaller number of lesions on MRI, but the number of clinical relapses remained the same on this short period of observation.

Two phase III studies are ongoing. The randomized DEFINE study, enrolled 1011 patients with relapsing-remitting MS treated with 480 mg/day and 720 mg/day of fumarate orally or placebo. The randomized CONFIRM study enrolled 1232 patients with relapsing-remitting MS treated with 480 mg/day and 720 mg/day of fumarate orally, placebo capsules orally, or Copaxone (11,12).

Many monoclonal antibodies, the object of study in MS, should inaugurate a second generation after natalizumab. These antibodies inhibit the activity of the mediators involved in the immune or inflammatory reactions taking a neutralizing or cytolytic action against the lymphocyte population. Phase II and III studies are ongoing for rituximab, ocrelizumab, alemtuzumab, ofatumumab, and daclizumab.

Rituximab is a humanized antibody recommended in the neoplastic pathology (lymphoma) as well as in inflammatory pathologies (rheumatoid arthritis). Directed against the CD20 antigen, its using causes a depletion of the B lymphocyte population.

A double-blind, phase II study, rituximab (1 g intravenous every other week) versus placebo included 104 patients with relapsing-remitting MS. The number of inflammatory lesions was reduced and the number of patients without any new lesions proved to be significantly smaller in treated patients compared with placebo, during the study and six months after the study ended. The frequency of relapses was also reduced. After 48 weeks 20.3% of the patients treated with rituximab presented relapses compared to the 40% of the placebo group. The results of this study were not compared to the ones obtained with natalizumab. There must be noted that rituximab stood at the origin of PML in patients treated for lupus.

Ocrelizumab, the entirely humanized form of rituximab, may be a treatment as active as rituximab but better

tolerated (13).

Alemtuzumab is an IgG humanized antibody directed against the CD52 glycoprotein present on the surface of the peripheral B and T lymphocytes. It is used in the treatment of chronic lymphocytic leukemia which is not responding to other treatments. A phase II study compared its efficacy to that of IFN-beta 1a (Rebif) in the treatment of the relapsing-remitting MS. The drugs were given for three years, alemtuzumab being more efficient than IFN in reduction of relapses rate and disability progression. If the efficacy of alemtuzumab seems superior to that of IFN, its side-effects are more severe (thrombocytopenia, purpura, infections, thyroid disorders). Phase III studies (CARE-MS I and CARE-MS II) shall analyze the safety and efficacy of alemtuzumab in patients with relapsing-remitting MS compared with IFN-beta 1a (Rebif) treatment (14). Daclizumab is a humanized monoclonal antibody (IgG1 subtype) anti-CD25 directed against the IL-2 receptor. The CHOICE study is a phase II, randomized, double-blind study that evaluated the efficacy and safety of daclizumab **versus** placebo when added to interferon beta therapy in patients with active MS. They received daclizumab 1mg/kg or 2 mg/kg subcutaneously every 2 weeks or placebo. The primary efficacy analysis at 24 weeks demonstrated a significant reduction in new or enlarged gadolinium enhancing lesions in the 2 mg/kg daclizumab group. A phase III study is ongoing in order to assess daclizumab in monotherapy versus Avonex (15).

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