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RESEARCH ARTICLE

MULTIPLE SCLEROSIS: FROM NEW APPROVED "DISEASE - MODIFYING" DRUGS TO TRIAL THERAPIES

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ABSTRACT

Background: Multiple sclerosis (MS) is a very common disease in the Western world and in Italy it is estimated that there are over one hundred thousand of patients, like HIV infection. In recent years, progress has been made with regard to lines of treatment and new drugs have been approved and already available and have changed the history of the disease making it favorable in most cases. **Methods**: the search for the articles to be included was conducted through the use of databases such as pubmed, scopus, researchgate, google scholar, by typing in keywords such as "multiple sclerosis therapies" the names of the new drugs and integrating with literature data. **Results**: The purpose of this article is to expose the characteristics of the most recent approved drugs, including oral ones, evaluating, based on clinical studies, their pharmacodynamic characteristics and adverse reactions, and finally to expose some of the compounds undergoing approval or innovative evaluation that in the coming months or years they may be commercially available. C**onclusions**: Disease-modifying therapies work both on the control of the underlying pathological process, limiting immune-mediated inflammation, and partly on the mechanism of neurodegeneration by slowing the progression. These drugs have shown remarkable results in decreasing the attack rate. However, there are still no definitive therapies, even if there are neuroprotective and remyelinating therapies in experimentation that seem to give very good results.

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INTRODUCTION

Multiple sclerosis (MS) is one of the most common chronic neurological diseases of young adults and it is estimated that in Italy it affects more than one hundred thousand people, with a double frequency in women, and in recent years considerable progress has been made in understanding the pathophysiological mechanisms of the basis of damage to the central nervous system (Ian Galea). It's a demyelinating disease with a typically remitting-relapsing (RR) course in over 80 % of cases, even if there are patients where, either primarily from the onset or after a variable period, a disability linked to the progression of the disease begins to accumulate with an accumulation of lesions and consequent neurodegeneration (Hans-Peter) (observational studies have shown that, after about 15 years from onset, about 50% of patients evolve in this form). However, there are also other clinical phenotypes of MS and they unfortunately do not respond to the first line drugs for which RR-MS is more responding.

In about 10-15 % of cases from the onset, there is a primary progression with no acute relapses or sudden worsening (Perini, 2019). Clinical prognostic markers have been identified that seem to characterize the patient with the greatest risk of progression, including male sex, age of onset over 40 years, multifocal presentation, cerebellar or sphincter onset, high frequency of relapses in the first attacks, incomplete recovery after the first attack (JONGEN) The cause of this disease is an overactivation of the cells of the immune system against an antigen expressed in myelin, a sheath that covers the axons, increasing the speed of conduction of the action potential and consequently leaving these structures similar to electric cables uncovered. consequently, they disperse the impulse causing conduction blocks responsible for clinical symptoms. The therapy of MS until a few decades ago involved treatments based exclusively on the use of steroids, powerful drugs still used in the treatment of acute attacks (relapses), in particular, high-dose methylprednisolone in a vein for 5 days (Perini, 2019).

However, steroids, while offering mild protection in the weeks following use, do not modify the long-term outcome by not interfering with the natural history of the disease, as well as being burdened by significant side effects in chronic use such as weight gain, metabolic disorders. and osteoporosis. Things changed thanks to the chance discovery that interferon beta (IFN), an antiviral drug, significantly reduces the clinical activity of the disease in terms of relapses and disabilities and was the first course-modifying drug and is still used on the front line in the remitting-relapsing forms (RR). Today various formulations are available, (IFN beta 1a and 1b for multiple weekly subcutaneous administration, IFN beta 1a weekly intramuscular and pegylated IFN beta 1a for subcutaneous administration every 2 weeks) (Comi, 2014) (https:// mymsaa.org/publications/msresearch-update-2020/temelimab/) however there are several problems related to the route of administration (subcutaneous or intramuscular injection) and chronic side effects such as dystyroidism, depression, cytopenias, hepatotoxicity, and flu-like syndrome. Since then, various immunomodulating drugs have been introduced which reduce disease activity by 30 to 70%. Approved treatments are commercially available today that target highly effective and specific monoclonal antibodies for immunological targets in MS. The first and still more effective today is natalizumab (Diluca, 2020), approved in 2006 and indicated as disease-modifying monotherapy in adults with highly active relapsing-remitting multiple sclerosis in the following patient groups (Comi, 2014):

People with high disease activity despite a full and adequate course of therapy with currently approved first-line immunomodulatory therapies for RR MS; people with rapidly evolving severe relapsing-remitting multiple sclerosis, defined by two or more disabling relapses in one year and with 1 or more Gadolinium-enhancing lesions on brain MRI. It's a humanized monoclonal antibody, produced in a cell line mouse by recombinant DNA technology, whose action consists in blocking the escape of T and B lymphocytes from blood vessels, inhibiting their entry into the nervous tissue. In particular, it is directed against integrin α4β1 (also called VLA-4) and acts by preventing lymphocyte adhesion and migration from the vascular bed to the site of inflammation. Integrins are a class of proteins involved in cell-cell and cell-extracellular matrix interaction; in particular, in the initiation of the immune process, they regulate the adhesion of T lymphocytes to endothelial cells and their passage through these, in the extracellular matrix and then they regulate the interaction between T lymphocytes and APCs (Antigen Presenting Cells, usually dendritic cells). Inhibition of the integrin prevents the activated T lymphocyte from meeting the APC and the immune response is not activated. In this way, activated T lymphocytes undergo apoptosis (Diluca, 2020). In clinical trials, natalizumab reduced the progression of disabling effects by about half of MS and has also reduced the number of MS attacks by about two-thirds. The drug has been shown to have good efficacy on relapses and the progression of disability in people with relapsing-remitting multiple sclerosis (RR). It's administered intravenously, once a month, in a hospital setting, over approximately 1 hour, patients should then be observed after the end of the infusion for any signs and symptoms of hypersensitivity reactions. It has long been available and reimbursable, authorized for patients who have not responded to a "complete and adequate" therapeutic course with the first-line immunomodulatory therapies currently approved for RR MS, or as an alternative to patients not previously treated with drugs immunomodulatory or immunosuppressive, but with a form of RR MS considered by the treating neurologist to be "severe and rapidly evolving". The therapy can only be carried out in the centers already identified by the Regions and already designated for the prescription of immunomodulating and immunosuppressive drugs and equipped with specifications listed in the "accreditation card" established by AIFA. The most common side effects reported by treated patients were headache (32%), nasopharyngitis (27%), fatigue (23%), urinary tract infection (16%), nausea (15%), arthralgia (14%), and dizziness (11%). Other less common effects reported by the pharmacovigilance cards are a reactivation of herpetic infections, anemia, general infusion reactions with flushing and low-grade fever, and skin rash. Multiple sclerosis centers must have experience in the diagnosis, therapy, and follow-up of patients with multiple sclerosis and have the possibility to perform an MRI examination with urgent characteristics (within 24-72 hours) in the suspicion of progressive multifocal leukoencephalopathy (PML). In addition to infusion-related side effects, cases of PML, a white matter disease due to the reactivation and virulent action of the JC virus, a papovavirus, have been described in pivotal studies. It occurs almost exclusively in people suffering from severe immunodeficiency. This virus has seroprevalence 90% of the population, has almost a latent origin of cases, and can give the disease only in the case of immunosuppression. Progressive multifocal leukoencephalopathy is characterized by nonspecific symptoms such as greater weakness, symptoms such as vision disturbances, behavioral or personality changes, memory and orientation disorders up to real pictures of mental confusion, epileptic seizures. Unfortunately, there are currently no specific antivirals; however, the symptoms may improve and the disease may stop with the recovery of the immunological capacity. If a person is being treated with natalizumab, the peripheral blood immune system has a normal response to infection, but the therapy blocks the entry into the system of cells capable of fighting JC virus infection. The prognosis of PML is very variable and can stress disability of extremely variable degrees, with clinical pictures from very mild to more severe, and in some cases death. In the case of PML that arises during treatment with natalizumab, early diagnosis and suspension of treatment are fundamental for a better prognosis: in fact, they significantly influence both the course that the infection will have and the degree of disability that can persist in people. - from very light paintings to more serious ones. It is possible to estimate the risk of PML by evaluating 3 parameters (Hutchinson, 2007): the presence of anti-JCV antibodies (people who test positive have a higher risk of developing PML; in these people, the estimated risk is 1 case of PML every 10,000 treated with natalizumab); duration of treatment (in JCV positive people, the risk increases with duration of treatment, particularly after the first 2 years of therapy) and prior treatment with immunosuppressive drugs. In people treated with natalizumab who tested positive for anti-JCV antibodies but who have not previously received immunosuppressive drug therapy, the level of antibody response (index) is associated with the level of risk of developing PML (i.e. higher antibody level there is a higher risk) (MAHAD, 2017). The drug is administered by infusion: the recommended dose is 12 mg for a day, administered in 2 courses of treatment. The initial course of treatment is for 5 consecutive days (total dose of 60 mg), while the second course, administered 12 months after the first, provides 12 mg for 3 consecutive days (total dose of 36 mg).

In October 2008, the results of the 3-year phase II study (CAMMS223), conducted on 334 people with relapsing-remitting multiple sclerosis, which compared two different dosages of alemtuzumab with interferon, were published in the New England Journal of Medicine (Coles, 2008). The analysis of the data obtained showed that after 36 months, people treated with alemtuzumab 12 mg/day had a 69% reduction in the risk of developing relapses and a 76% reduction in accumulation on sustained disability compared to the group treated with interferon. Subsequently, in 2009, during the American Academy of Neurology, the researchers announced further processing of the data from the CAMMS223 study, which showed, in the first months of treatment with alemtuzumab, a notable reduction in disability, defined by a decrease of one score point on the EDSS scale for more than six months, twice as much as in those using interferon beta-1a. Researchers suggested there that alemtuzumab treatment could halt the progression of disability and stably reverse the pre-existing neurological deficit and that further phase III studies would be developed for this reason. This was followed in 2012 by the publication in Neurology of the 5-year extension of the CAMMS 223 study, which substantially confirms what was observed in the 3-year observation. Also in 2012, the results of two phase III studies, called CARE-MS I and CARE-MS II, were published in the scientific journal Lancet. In particular, the CARE-MS I study (also known as CAMMS 323, Comparison of Alemtuzumab and interferon Efficacy in Multiple Sclerosis), aimed to evaluate the efficacy and safety of alemtuzumab at a dose of 12 mg/day alone in the treatment of relapsing-remitting MS, as compared with interferon beta-1a, three times a week, subcutaneously in a population similar to that studied in CAMMS 223 but with a longer history of the disease (<5 aa). The two-year study showed that alemtuzumab reduced the frequency of relapses by about 55% compared to those taking interferon. In addition, 78% of people taking alemtuzumab had no relapse during the two years of the study compared with 59% in the interferon group. There had been no significant effects on the progression of disability 8% of those who had taken alemtuzumab and 11% of those who had taken interferon showed a worsening in disability. The CARE-MS II study (also known as CAMMS 324, Comparison of Alemtuzumab and interferon Efficacy in Multiple Sclerosis), aimed to establish the efficacy and safety of two different strengths of alemtuzumab as a treatment for relapsing-remitting MS in comparison with Rebif®, in a population of patients who had a longer disease duration (<10), and EDSS <5 and who had not responded to previous immunomodulatory therapy. The study observed 667 people who continued to relapse despite treatment with beta interferon. The frequency of relapses of those taking alemtuzumab was reduced by 49% compared to those taking interferon and a significant reduction in the accumulation of sustained disability assessed at 6 months of 42% was also observed. 65% of people on alemtuzumab had no relapse during the two years of treatment compared with the interferon group (47%). In addition, there was a small improvement in the EDSS score in the alemtuzumab group compared with a small worsening in the EDSS score in the interferon group. The long-term results of an open-label study conducted on 87 patients observed for an average period of 7 years and which therefore constitutes the longest-lasting clinical experience in the use of alemtuzumab in sclerosis have recently been published by the Cambridge group. multiple; also in this population, which differs from that observed in clinical studies, alemtuzumab confirms its ability to significantly control relapses, achieving improvement or stabilization of disability in about 60% of patients. The safety profile is favorable even if in some patients, in addition to the classic infusion reactions, there has been an increased risk of other autoimmune diseases, such as idiopathic thrombocytopenic purpura (ITP), anti-glomerular basement membrane antibody disease (anti-GBM).) and autoimmune pathologies affecting the thyroid gland. Therefore periodic checks, such as blood count, serum creatinine, and urinalysis should be performed before the start of treatment and subsequently at monthly intervals for the 48 months following the last infusion, while thyroid function tests should be performed every 3 months, again for 48 months from the last infusion. To these monoclonal antibodies, in the last years, oral drugs with an innovative action profile have been marketed. Fingolimod was the first oral drug to be approved for RRMS and is reimbursable in Italy for highly active forms of the disease. It is a modulator of sphingosine, an antagonist of the receptor 1 expressed on lymphocytes, it reduces their migration in the CNS by trapping them inside the lymph nodes with a prevalent action on the memory T ones. Compared to placebo, it reduces relapses by over 50% but the first administration requires ECG monitoring because it can induce bradyarrhythmias (Sanford, 2014). It can also cause increased transaminases, leukopenia, and cutaneous neoplasms. Recently were then added two orally active drugs, cladribine, and dimethyl fumarate. Cladribine is a second-line drug indicated for adult patients with relapsing multiple sclerosis (MS) with high disease activity. From 2019 it's commercially available and refundable. Chemically it is an analog of deoxyadenosine and belongs to the class of antimetabolites. Once it enters the cell, being resistant to the degradative action of adenosine-deamidase, it accumulates and is transformed into the active triphosphorylatedform which interferes with DNA synthesis inducing apoptosis of the cell, especially in the lymphocytes. It is administered orally in 2 cycles, each lasting 4-5 days, based on body weight, carried out one year apart. The treatment induces a high reduction in T and B lymphocyte counts and reduces the frequency of attacks by 58% on average and the progression of disability by 47%. Induced lymphopenia causes a higher incidence of herpetic infections in particular. Dimethyl fumarate, on the other hand, is first-line therapy and is an ester of fumaric acid, used in the treatment of psoriasis. The mechanism of action is very complex and only partially clarified since it inhibits the proinflammatory activity of NFKB and activates the anti-inflammatory activity of NRF2. It is administered orally twice a day and can cause intestinal disorders and flushing. Cases of severe lymphopenia with associated PML have been reported.

MECHANISMS OF ACTION OF NEW ORAL DRUGS IN MS: Fingolimod acts on the system of sphingosine 1 phosphate (S1P), a major unsaturated chain amino alcohol constituent of sphingolipids of cell membranes. In the CNS sphingomyelin, cerebrosides and gangliosides are the main sphingolipids present and all derive from ceramide, in turn, derived from sphingosine (also present intracellularly due to the catabolism of the preceding ones). among all the metabolites of the sphingolipids, research has focused above all on S1P, capable of regulating various intracellular functions, survival, and proliferation, promoted by the phosphorylation of sphingosine by SphK1. Moreover S1P functions as a cytoplasmic messenger for the activation of membrane receptors coupled to g proteins (S1P is extruded from the cell through ATP-binding transporters and, once outside, binds to these receptors in an autocrine or paracrine

modality) (Hauser, 2016). The circulation of naive B and T lymphocytes between blood and lymphoid organs is regulated by S1P, whose activation of the type 1 receptor expressed by the lymphocyte favors its exit from the lymph nodes.

When the naive cell is activated by the antigen, the S1P receptor is temporarily sequestered in the cytoplasm to keep the cell inside the lymph node and favor its clonal expansion. In addition to regulating lymphocyte trafficking, sphingosine promotes the survival of lymphocytes by protecting them from apoptosis. All CNS cells have S1P receptors including astrocytes and oligodendrocytes. Fingolimod, through internalization of the S1P receptor 1, increases the retention of autoreactive lymphocytes in the lymphoid organs by reducing their migration into the brain and this effect only affects naive and memory T cells while sparing peripheral populations. Dimethyl fumarate, on the other hand, is a derivative of fumaric acid, an intermediate in the cycle of tricarboxylic acids, capable of influencing the response of nerve cells to oxidative stress. It increases the expression of a transcription factor called Nrf2 which controls the synthesis of many intracellular enzymes with a detoxifying function. Normally Nrf2 is localized in the cytoplasm and forms a trimer with 2 molecules of a protein adapter whose cysteine residues act as a sensor of the oxidative state and, if exposed to an electrophilic environment, release Nrf2 which translocates into the nucleus and is phosphorylated with an increase in transcription of enzymes that detoxify ROS (free radicals) and increase glutathione levels. The fumarate activates this system by forming complexes with glutathione that reduce the available levels, providing a mild toxic stimulus to the cell that responds by activating this protective mechanism. The clinical effect of dimethyl fumarate is to trigger apoptosis of reactive T lymphocytes and to regulate T differentiation. it also exhibits a neuroprotective effect (Di Nuzzo, 2017; GeNeuro).

Cladribine is chemotherapy and immunosuppressive drug used initially for the treatment of hairy cell leukemia. Its chemical name is 2-chlorodeoxyadenosine (2CDA). As an analog of purines, it chemically mimics the nucleotide adenosine and inhibits the enzyme adenosine deaminase, which intervenes in the cell's ability to process DNA. It is easily destroyed by cells except for blood cells, thus ensuring few side effects and great precision in the therapeutic target. it is administered parenterally in the treatment of leukemia and tablets only for RRMS. The recommended dose is 3.5 mg/kg body weight over 2 years, given as 1 treatment cycle per year where Each cycle consists of 2 weeks of treatment, one at the beginning of the first month and one at the beginning of the second month of the corresponding treatment year. Each week of treatment consists of 4 or 5 days in which the patient takes one or two tablets as a single daily dose, based on body weight. After the completion of the 2 cycles, no further administration is required in the following 3 or 4 years. A replacement of the chlorine in the ring purine protects cladribine from degradation by adenosine deaminase and thus increases the intracellular residence time of the prodrug cladribine. The subsequent phosphorylation of the cladribine to the active triphosphate form, 2-chlorodeoxyadenosine triphosphate (Cd-ATP), is particularly effective in lymphocytes, due to the constitutively elevated levels of deoxycytidine kinase (DCK) and relatively low levels of 5'-nucleotidase (5'-NTase). A high DCK / 5'-NTase ratio favors the accumulation of Cd-ATP and makes lymphocytes particularly susceptible to cell death. Because of a lower DCK / 5'-NTase ratio, other cells of bone marrow origin are less affected than lymphocytes. DCK is the enzyme limiting the rate of conversion of the prodrug cladribine into the form of active triphosphate, resulting in selective depletion of dividing and non-dividing T and B cells. The main mechanism of action of Cd-ATP that induces apoptosis has direct and indirect effects on DNA synthesis and mitochondrial function. In dividing cells, Cd-ATP interferes with DNA synthesis through the inhibition of ribonucleotide reductase and competes with deoxyadenosine triphosphate for incorporation into DNA by DNA polymerases. In resting cells, Cladribine induces single-stranded DNA breaks, rapid consumption of nicotinamide adenine dinucleotide, ATP depletion, and cell death. It has been shown that cladribine exerts a long-term effect through its action on a target preferential represented by lymphocytes and autoimmune processes involved in the pathophysiology of SM. Across studies, the largest proportion of patients with grade 3 or 4 (<500 to 200 cells / mm^3 or <200 cells / mm^3) was observed 2 months after the first dose of cladribine each year, indicating that there is a time gap between plasma concentrations of cladribine and maximal hematological effect Treatment with oral cladribine results in rapid reduction of CD4 + and CD8 + T cells circulating. CD8 + T cells exhibit less marked reduction and faster recovery compared to CD4 + T cells, resulting in a temporary reduction in the CD4 / CD8 ratio.

New drugs or interesting new combinations are currently being tested. Among the various molecules undergoing studies, simvastatin should be mentioned, an oral drug where anti-inflammatory and neuroprotective effects are exploited in the field of multiple sclerosis. For example, the combination of simvastatin with traditional interferon-based therapies has been studied and the studies differ. The SIMCOMBIN Study is a multi-center, placebo-controlled randomized phase 4 trial conducted on 307 naïve-treatment people, where the authors set out to verify the safety, tolerability, and efficacy of low doses of atorvastatin, as a combined treatment with beta-interferon 1a (Sorensen, 2011). After starting treatment with interferon beta, patients were randomly assigned (in computer-generated blocks of four patients) to simvastatin 80 mg per day or placebo for 1-3 years. Patients and treating and evaluating physicians were masked to treatment allocation. The primary outcome measure was the annual rate of documented relapses. Patients were randomly assigned to interferon beta plus simvastatin (n=151) or plus placebo (n=156); the study found no beneficial effect of simvastatin as add-on therapy to interferon beta-1a but they can not exclude that combination of other statins with other disease-modifying drugs still could be beneficial. In a review published in 2014, the authors analyzed the main mechanisms potentially related to the neuroprotective properties of statins such as antioxidant effects, regulation of nitric oxide production, and modulation of the enzyme eNOS and matrix metalloproteases (MMPs) that play an important role in the immunomodulatory effects of statins.From the analysis of the various studies under review, the immunomodulatory properties of statins emerged in some studies conducted on animal models, which could bring a benefit in the treatment of neuro-inflammatory disorders such as MS. In addition, a small open-label study with simvastatin (80mg per day for 6 months) in relapsing-remitting MS showed a decrease of approximately 45 percent in mean number and mean volume from the analysis of magnetic resonance data. of contrast-enhancing lesions in treated people.

An Iranian study of combined therapy between interferon beta 1a and atorvastatin involved 95 people with MS, divided into two groups. the first in treatment with intramuscular interferon beta-1a, the second in treatment with atorvastatin (40mg per day) associated with interferon beta-1a for 18 months. No significant differences were observed between the two groups regarding clinical parameters assessed by EDSS and non-magnetic resonance imaging, while some hematochemical parameters, including IL-17, TNF-α, and lymphocyte proliferation, were significantly decreased compared to the control group. In 2019, Diroximel fumarate was approved in the USA, a molecule similar to dimethyl fumarate and in the human body the two molecules are converted into monomethyl fumarate, however, it is believed that diroximel fumarate may have fewer side effects on the gastrointestinal level(12); is marketed in tablets to be taken twice a day and the most frequently reported side effects are flushing, abdominal pain, diarrhea, and nausea (events reported for dimethyl fumarate which is the same metabolite as diroximel fumarate but to a greater extent). In January 2021 the manufacturer applied for authorization of the drug, as a treatment for relapsing-remitting MS, to the EMA. Another oral drug available shortly will be Ozanimod, a sphingosine 1-phosphate receptor modulator (S1PR), in tablets to be taken once a day. Compared to fingolimod, the initial temporary lowering of the heart rate should not occur (JONGEN); 1346 people with relapsing MS were involved in the Phase III Sunbeam study. Participants took one of two doses of ozanimod or interferon beta 1a for one year. For the group taking 0.5 mg of ozanimod, the annual relapse rate was 0.24, a 31% reduction compared to interferon. For the group taking 1.0 mg of ozanimod, the relapse rate was 0.18, which represents a 48% reduction compared to interferon. Compared to interferon, both dosages of ozanimod also reduced the number of new active lesions observed on MRI. authorized by the FDA in March 2020, it can be prescribed for relapsing forms of MS including CIS, classic relapsing-remitting forms and secondary progressive forms in which disease activity is present (Swallow, 2020).

In November 2020 AIFA entered ozanimod in the class of drugs called C, dedicated to drugs not yet evaluated for reimbursement purposes. Ponesimod also belongs to the same class of drugs to which fingolimod belongs, therefore it acts by binding to the sphingosine 1-phosphate receptor (S1P) which is present on the surface of lymphocytes, binding to them to ensure that they are retained in the lymph nodes and therefore cannot reach the central nervous system. It is taken in tablets, one a day, while the experimental therapies for the re-induction of remyelination seem very interesting, including a derivative of vitamin A, Bexarotene, the object of phase 2 study, and other molecules such as Temelimab, Ibudilast, clemastina, bexaroteneand opicinumab. Temelimab is a monoclonal antibody designed to prevent inflammation and damage to the myelin sheath that insulates nerve cells by attacking the envelope protein (Env) of the endogenous human retrovirus MSRV. In fact, MS is a disease in whose pathogenesis, which still remains in some respects unknown, various infectious factors, especially viral, have been proposed as co-factors in the abnormal immunological hyperactivation, but the exact causal relationship between viral infections and this pathology still remains to be understood. Among the proposed factors are the Epstein Barr virus (EBV) and two members of the W family of human endogenous retroviruses (HERV), the multiple sclerosis retrovirus (MSRV) and the element ERVW-1, which expresses only the protein of envelope (pericapsid) of the virus, called Syncithin-1. As for the EBV virus, there are many studies that support its association with MS. In fact, the risk of onset is low in subjects who are serologically EBV-negative, and the scientific community agrees on two links between EBV and MS:

- Having become late infected with EBV, becoming ill with infectious mononucleosis (associated with a 2-4 fold increase in MS risk)(24)
- Having had, before the onset of MS, a high titre of antibodies directed against EBV nuclear antigens (EBNA, Epstein-Barr nuclear antigens).

One potential cause of demyelination attacks is the activation of MS-associated retrovirus or MSRV, a virus that is commonly present, but inactive, in the genome. When active, MSRV produces a protein called MSRV-envelope protein, or MSRV-Env, which triggers an immune response. The presence of MSRV-Env in MS has been confirmed in MS brain lesions. Temelimab is an antibody that researchers designed to specifically target MSRV-Env, preventing it from inducing an immune response. This drugis an IgG4 totally human monoclonal antibody that blocks the effect of a protein found in MS brain lesions who have been shown to stress inflammation and reduce remyelination. Clinical trial results suggest that this drug may promote remyelination.Temelimab, like all monoclonal antibody, is administered parenterally once a month and more importantly, to date, patients who have taken it have reported no significant side effects(15). However, we are obviously always talking about phase II therapies, as they are subject to continuous development, although they have proved very effective in reducing relapses but with little effect on the long-term course of disability(22). What will certainly need to be changed in phase 3 will be the administration of the optimal dose, the key image of this analysis. Indeed, in this study, it was found that temelimab would likely mask the neuroprotective effects of this drug in patients (Anti) (Low Temelimab).

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