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Original Review Article

ROLE OF ANTI-INFLAMMATORY AGENTS AS A TREATMENT OF MULTIPLE SCLEROSIS

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ABSTRACT

Multiple sclerosis (MS) is a neurodegenerative disease in which the immune system recognizes proteins of the myelin sheath as antigenic, thus initiating an inflammatory reaction in the central nervous system. It is characterized by intermittent or chronic damage to the myelin sheaths (demyelination), focal inflammation and axonal degeneration Inflammation has always been as the pathophysiology of multiple sclerosis. The present pharmacological treatment of MS administration of immunomodulatory and anti-inflammatory drugs, which are only palliative and slow progress of the disease. Infection, trauma or autoimmune inflammation in experimental allergic multiple sclerosis and they are competent presenters of antigen and interact with T cells recruited to the inflamed CNS. Symptoms of inflammation in general and more specifically in multiple sclerosis, a demyelinating, autoimmune disease characterized by inflammation of the central nervous system (CNS). Inflammation has always been thought of as detrimental in the pathophysiology of multiple sclerosis. However, emerging genetic data, magnetic-resonance-imaging studies, and immunopathological evidence challenge this simplistic view. Inflammatory cells normally occurs via emigration or insitu apoptosis. Characterization of the inflammatory infiltrates present in MS brain and spinal cord tissue. Studies in of myelin proteins can become immune system targets resulting in demyelination, and these models have also served to define multiple immunological mechanisms of disease. Primary inflammatory cytokines and chemokines with a proretention activity have been found in active MS. Plaquesfocal inflammation and axonal degeneration. During the early relapsing/remitting stages of MS, myelin can regenerate, but as the disease progresses the remyelination of axons becomes insufficient, leading to impaired axon conduction, neurodegeneration and the worsening of symptoms. The rationale to influence immunological activity in MS is to suppress myelin and axonal damage and thus to prevent clinicaldisability.

Key Word: Anti-inflammatory, multiple sclerosis

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Introduction

Multiple sclerosis (MS) is the most common immune mediated disease of central nervous system (CNS)[1]. Resulting in disability in younger adulthood and affects many million people worldwide. Multiple sclerosis is the commonest chronic inflammatory disorder of the CNS. The disease is characterized pathologically by multifocal areas of inflammatory demyelination although axons are generally spared in the initial phase of the disease [2-5]. Demyelinated areas in the CNS of patients with multiple sclerosis are characterized by inflammatory infiltrates that contain blood-derived myelin specific T cells, B cells that secrete antibodies to myelin components, and a multitude of non-specific, effector mononuclear cells. This pathogenetic description has lead to the concluded that MS is a chronic, inflammatory, autoimmune, demyelinating disease of the CNS [6-8]. Inflammation has always been thought of as in the pathophysiology of multiple sclerosis. The evidence leads to the conclusion that inflammation is regulated, and that its net effect may be beneficial in MS, thus explaining some of the results from recent trials of anti-inflammatory agents. The application of anti-inflammatory drugs to treat MS could not be appropriate in all cases. Predictable identification of the inflammatory pathways to be targeted in the different phases of the disease and the timing of such interventions are therefore crucial. However, emerging genetic data, magnetic-resonance-imaging studies, and immune-pathological evidence challenge this simplistic view. Demyelinated areas in the CNS of patients with multiple sclerosis (MS) are characterised by inflammatory infiltrates that contain blood-derived myelin specific T cells, B cells that secrete antibodies to myelin components, and a multitude of non-specific, effectors mononuclear cells. This pathogenetic description has lead to the conclued that MS is a chronic, inflammatory, autoimmune, demyelinating disease of the CNS. From an immunological point of view, chronic inflammation in MS can be thought of as an inflammatory process with a disordered resolution phase [9-12]. Activation of T cells enables their transmigration through the blood–brain barrier to the target tissue, an intricate cascade of events governed by adhesion molecules, chemotactic factors and migration promoters. Reactivated in situ, these T cells of both CD4 T helper and CD8 cytotoxic phenotype release pro-inflammatory Th1 cytokines and orchestrate the degradation of the myelin sheath via various types of resident andimmigrated immune cells and soluble toxic mediators. The T-cell and macrophage-mediated demyelination or antibody-mediated, complement-dependent demyelination [13-15]. MS is a very heterogeneous disease with very diverse pathological and clinical manifestations. Some of the clinical symptoms include loss of balance and coordination, visual and sensory impairment, fatigue, and cognitive difficulties [16]. The persistence of inflammatory CNS infiltrates could be caused by long lasting “danger signals”. Although many viruses have been implicated as possible danger signals in MS, there is no conclusive evidence that any pathogens have such a role. Chronic inflammation in MS from in-situ production of proretention and prosurvival factors that prevent the clearance of blood-borne inflammatory cells that have invaded the CNS. The clearance of inflammatory cells normally occurs via emigration or insitu apoptosis [17-22]. The most common form of the disease is relapsing–remitting MS (RRMS), which is characterized by a series of episodes of neurological dysfunction, known as MS relapses, exacerbations, or attacks. These relapses are separated by periods of remission during which clinical recovery may or may not be complete. Over time, incomplete recovery from relapses leads to increasing permanent neurological disability In contrast to many degenerative diseases; the average age of onset for MS is relatively early (20–40 years) [23]. Immunomodulatory drugs used to treat MS decrease the clinical relapse rate and

accompanying inflammation within the central nervous system. Initially approved therapies were all injectable (either subcutaneous or parenteral) and inc lude interferon-β (IFNβ), glatiramer acetate (GA), natalizumab, and mitoxantrone[24].

Role of T-cell and B-cell in MS

T (Treg) cells migrate into both inflammatory sites and draining lymph nodes (LNs) during an immune response, and have unique and overlapping functions in each location.[25-26] A recent study has suggested [27-28] that Treg cell suppressive activity is more important at the site of tissue inflammation than in draining LNs,[29] whereas the initial interactions of Treg cell precursors with antigen in draining LNs are important for induction of aTreg cells and activation of both nTreg and aTreg cells for their suppressive function [30]. Autoimmune diseases, including MS, are characterized by T effector cell migration and accumulation at the pathological site. Treg cells also accumulate within the murine central nervous system (CNS) during experimental autoimmune encephalomyelitis (EAE)], an animal model for MS.Activated B cells and T cells that recognize foreign protein antigen in the peripheral lymphoid tissue come together to initiate humoral immune response[31]. Within one or two days of antigen administration, naïve CD4+ T cells recognize antigen presented activate transcription of immunoglobulin genes. Some of the B cells that have proliferated differentiate into effector cells that actively secrete antibodies.

Magnetic resonance imaging in MS

Magnetic resonance imaging (MRI) is the most sensitive ability para-clinical parameter in diagnosing MS [32-33]. Magnetic resonance imaging (MRI) role in the diagnosis and management of multiple sclerosis (MS), since the beginning of its application by Young et al. in this field [34-35]. Multiple sclerosis (MS) is a chronic inflammatory demyelinating disorder of the central nervous system. The histo-pathological and physiological hallmark of this disease is the demyelinated plaque, which is associated with parenchymal inflammatory cell infiltrates in the acute disease stage. There is a variable extent of axonal injuryand inflammation between patients, and several markers of tissue destruction have been established in magnetic resonance imaging (MRI) studies.[36-37] It is conceivable that one treatment might suppress demyelination (thus producing clinical stability), but not inflammation (which produces continuing gadolinium enhancement on MRI). Conversely, another treatment may suppress inflammation (and hence stop gadolinium enhancement), but not demyelination .[38]

Pathophysiology of MS

The branch of medicine concerned with the cause, origin, and nature of disease, including the changes occurring as a result of disease .The axonal loss are prominent pathological features and therefore it is conceivable that atrophy is largely explained by loss of these tissue components [39]. Pathological hallmarks of cortical GM lesions seem to be largely restricted to demyelination and occasionally aminor microglial reaction. Thus, the pathology of cortical lesions strikingly differs from that of WM lesions. Lymphocyte infiltration, complement deposition, and blood– brain barrier (BBB) disruption, all typical pathological hallmarks of WM lesions, are not usually found in cortical lesions [40–42]. Thepathological subtypes of MS do not segregate with the clinical evolution of the disease, such as the primary progressive or secondary progressive vs. the relapsing–remitting variant [43].

Anti –inflammatory agent an MS

1. Interferon beta

Interferon beta-1a (also interferon beta-1-alpha) is a drug used to treat multiple sclerosis (MS) [44]. It is produced by mammalian cells, while Interferon beta-1b is produced in modified E. coli. Interferons have been shown to produce about an 18–38% reduction in the rate of MS relapses [45]. There is currently no cure for MS. Starting a course of interferons early may slow its progress [46]. Interferon beta is anti-inflammatory agents in the brain, and reduces

the number of inflammatory cells that cross the blood brain barrier [47]. Therapy with interferon beta leads to a reduction of neuron inflammation Moreover, it is also thought to increase the production of nerve growth factor and improve neuronal survival. Interferon therapy for relapsing-remitting multiple sclerosis (MS). efficacy of beta interferon in the treatment of MS rests on seven large, randomized, placebo-controlled trials (RCTs), each including over 300 patients. Three of these trials [48-49] studied patients with relapsing–remitting (RR) MS and four studied patients with secondary progressive (SP) MS [50-58]. The beta interferons work by reducing the inflammatory process that characterizes MS. Such inflammation usually precedes an MS relapse. However, the precise mode of action of these disease-modifying agents on immunological mechanisms remains uncertain [59-64].

2. Natalizumab

Natalizumab is a humanized anti-α-4 integrin monoclonal antibody that prevents the adhesion of lymphocytes and monocytes to the vascular endothelium and their migration into parenchyma and the demyelinated plaque formation and transection of axons; and a widespread nervous tissue destruction leading to an axonal and neuronal loss. . Natalizumab is believed to work by reducing the ability and capability of inflammatory immune cells to attach to and pass through the cell layers lining the intestines and blood–brain barrier [65-66]. Natalizumab has proven effective in treating the symptoms of both diseases, preventing relapse, vision loss, cognitive decline and significantly improving quality of life in people with multiple sclerosis, as well as increasing rates of remission.Natalizumab is an alpha-4-integrin antagonist approved as monotherapy for patients with relapsing forms of MS, based on demonstrated efficacy in two phase III trials, AFFIRM and SENTINEL, over relapses and disability [67-68], and subrogate MRI markers of inflammation, like gadolinium-enhancing lesions (CEL), new T2 lesions and T2-lesion volume (T2LV); or over axonal damage, like new T1-hypointense lesions and T1-hypointense lesion volume [69]. The first drug developed in the class of selective adhesion molecule inhibitors. The α4-integrin is required for white blood cells to move into organs, and natalizumab's is believed to be the prevention of immune cells from crossing blood vessel walls to reach affected organs. These antibodies with the trafficking of leukocytes across the bloodebrain barrier, thereby reducing the inflammatory component of MS. Natalizumab has provided further hope to patients with MS; in pivotal trials natalizumab was associated with a sharp reduction in annualized relapse rate and appeared to slow disease progression[70].

3. Teriflunomide

Teriflunomide is the active metabolite of leflunomide [71]. Teriflunomide was investi-gated in the l TEMSO as a medication for multiple sclerosis (MS). "although permanent discontinuations [of therapy] were substantially less common among MS patients who received teriflunomide compared with interferon beta-1a, substitute were more common with teriflunomide"[72] . Teriflunomide is an immunomodulatory drug inhibiting pyrimidine de novo synthesis by blocking the enzyme dihydroorotate dehydrogenase. Teriflunomide inhibits rapidly dividing cells, including activated T cells, which are thought to drive the disease process in MS. Teriflunomide may decrease the risk of infections compared to chemotherapy-like drugs because of its more-limited effects on the immune system[73]. teriflunomide blocks the transcription factor NF-κB. It also inhibits tyrosine kinase enzymes, but only in high doses not clinically used [74]. Teriflunomide in MS therapy is strongly dependent on the safety and tolerability characteristics. As mentioned earlier, in teriflunomide trials AEs all treatment and placebo groups. Common adverse effects of teriflunomide include gastrointestinal symptoms (diarrhea, dyspepsia, nausea, vomiting, abdominal pain, and oral ulcers), increased levels of liver enzymes, skin rashes, weight loss, hair thinning, infections, and hypertension [75]. In the Phase II trial of teriflunomide as monotherapy, despite the

decrease in leukocytes seen in the active drug groups, infection rates were similar among drug and placebo groups and there were no discontinuations of therapy owing to leukopenia[76]. However, a higher rate of infections in treated patients was seen when teriflunomide was combined with IFNβ, but not in combination therapy with GA[77].In the TEMSO study, mean reductions in lymphocyte and neutrophil counts were small (#15%) and reversible.

4. **Glatiramer acetate**

Glatiramer acetate is an immunomodulator drug currently used to treat multiple sclerosis. It is a random polymer of four amino acids found in myelin basic protein, namely glutamic acid, lysine, alanine, and tyrosine, and may work as a decoy for the immune system. Glatiramer acetate for reducing the frequency of relapses, but not for reducing the progression of disability. Observational studies, but not randomized controlled trials, suggest that it may reduce progression of disability.Although the clinical definition of multiple sclerosis requires two or more episodes of symptoms and signs, glatiramer acetate is approved for treatment after single episodes. It is also used to treat relapsing-remitting multiple sclerosis. The mechanism of action for glatiramer is the. T cells from pro-inflammatory Th1 cells to regulatory Th2 cells that suppress the inflammatory response[78]. Given its resemblance to myelin basic protein, glatiramer may also act as a sort of decoy, diverting an autoimmune response against myelin. The integrity of the blood–brain barrier, however, is not appreciably affected by glatiramer, at least not in the early stages of treatment. Glatiramer acetate has been shown in clinical trials to reduce the number and severity of exacerbations [79]. The mechanism(s) by which glatiramer acetate its effects in patients with Multiple Sclerosis (MS) is not fully elucidated. However, it is thought to act by modifying immune processes that are currently believed to be responsible for the pathophysiology of MS. the pathogenesis of experimental autoimmune encephalomyelitis (EAE), a condition induced in several animal species through immunization against central nervous system derived material containing myelin and often used as an experimental animal model of MS. Studies in animals and in vitro systems suggest that upon its administration, glatiramer acetate-specific suppressor T-cells are induced and activated in the periphery[80].

5.Mitoxantrone-

Mitoxantrone is an anthracenedione derivate which is structurally related to the anthracycline derivates. It was synthesised in an effort to maintain or even improve anthracycline antitumour activity, but with reduced side-effects, particularly cardiotoxicity [81]. Mitoxantrone hydrochloride (Novantrone) is an anthracenedione that has been used as an antineoplastic agent to treat hormone-refractory prostate cancer and acute nonlymphocytic leukemia in adults. It exerts its antineoplastic action by intercalating into DNA and producing both DNA strand-breaks and interstrand cross-links; it also interferes with RNA synthesis and markedly inhibits the enzyme topoisomerase II, which aids in the DNA repair process[82-85]. In the treatment of MS, mitoxantrone represents the latest in a long line of general immunosuppressive agents studied in this disease. [86-91].

Conclusion

Immuno- pathogenetic aspects of MS remain to be clarified. How- ever, recent advances in immunotherapeutic techniques hold out the promise for new horizons in the management of MS with non-toxic, non-immunosuppressive drugs. In com-parison with other alternative treatments used to treat MS,GAappears to be as good a therapy for both benefits and risks as interferon beta-1a and interferon beta-1b. To better individualize patient management and direct expensive therapies to those who benefit from them most, clinical and immunological baseline markers and treatment responsepredictors are needed.

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