Immunological Disorders and Immunotherapy

Heuser, et al., Immunol Disord Immunother 2016, 1:3

Mini Review Open Access

The "Efficacy Approach": Infusion Therapies in the Treatment of Relapsing-Remitting Multiple Sclerosis

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Rec date: October 04, 2016, **Acc date: October** 24, 2016**, Pub date: October** 26, 2016

Abstract

Multiple sclerosis (MS) is among the most common causes of neurological disability in young adults. As an immune-mediated inflammatory demyelinating disease of the central nervous system (CNS), treatment is aimed at decreasing the rate of relapse and slowing the accumulation of brain lesions on MRI readings. A number of immune-modulatory treatments are currently available that effectively reduce the relapse rate, however they are not curative. An algorithm presently exists, but the choice of specific agent should be individualized according to disease activity, patient values, and preferences. This review will focus on the use of infusion therapies that have been studied for the treatment of relapsing-remitting multiple sclerosis (RRMS). Natalizumab and Alemtuzumab have been studied extensively in phase III clinical trials and are considered to be highly effective for the treatment of RRMS. In comparison, mitoxantrone, which is an immunomodulary agent used in relapsing-remitting and progressive forms of MS, has limitations due to the risk for cardiac toxicity and limited evidence of clinical benefit. Infusion therapies with Natalizumab and Alemtuzumab have truly changed the treatment of RRMS and their significant advantages and benefits should not be discounted.

Keywords: Multiple sclerosis; Treatment; Infusion therapies; Relapsing-remitting multiple sclerosis

Introduction

Multiple sclerosis (MS) is a chronic autoimmune neurological disease of the CNS affecting the myelin and is considered to be the most common immune-mediated inflammatory demyelinating disease of the CNS [1]. MS attacks the myelinated axons in the CNS resulting in the destruction and dysfunction of the myelin and axons. As MS is characterized as an autoimmune disease, the pathology revolves around the infiltration of immune cells across the blood brain barrier (BBB) promoting inflammation, demyelination, gliosis, and neuroaxonal degeneration, resulting in the development of lesions in the CNS and the disruption of neuronal signaling [2]. Consequently, many of these individuals who have MS will inadvertently experience progressive neurological deficits that are reversible at first but progressively develop to become irreversible. Individuals with MS who are symptomatic will often experience sensory disturbances such as paresthesias, dysesthesias, diplopia, ataxia, vertigo, and bladder irregularities. Furthermore, these sensory disturbances may evolve into chronic neuropathic pain, trigeminal neuralgia, optic neuritis and complete or partial loss of vision [1]. MS is a chronic disease that disables and debilitates an individual resulting in a decrease quality of life. Therefore, it is necessary to manage patients who are diagnosed with this condition. Although there is no cure-all treatment available, there are disease modifying drugs that provide symptomatic relief, reduce duration of acute exacerbations, and prevent reoccurrences. More importantly these medications can reduce the severity and progression of the relapsing forms of MS.

Natalizumab

Natalizumab (Tysabri®), a recombinant, humanized antibody, is a new disease modifying therapy for the treatment of RRMS. Natalizumab is a selective adhesion molecule inhibitor that binds to α4β1-integrin (a surface adhesion molecule found on leukocytes) and blocks its interaction with vascular cell adhesion molecule-1 (VCAM-1). As a result, leukocyte migration into brain tissue is inhibited, reducing inflammation and preventing the formation of lesions [3]. There are two randomized phase III trials of natalizumab in patients with relapsing MS, which assessed the drugs clinical efficacy in the management of MS. The AFFIRM study concluded that natalizumab significant improved quality of life by reducing risk of sustained progression of disability and rate of relapses in comparison to placebo [4]. Furthermore, the SENTINEL study compared the addition of natalizumab to standard regimen of intramuscular interferon β-1a vs. intramuscular interferon β-1a (IFNβ-1a) alone. The study concluded that the addition of natalizumab was significantly more efficacious than IFNβ-1a alone [5]. In all phase II trials, natalizumab was well tolerated and had similar side effect profile to that of placebo. In the AFFIRM trial, the incidence rates of adverse drug events were not significantly different between natalizumab and placebo except for fatigue (27% vs. 21%, respectively; $p<0.05$) and allergic reactions (9% vs. 4%; $p<0.05$). On the other hand, in SENTINEL, combination therapy with natalizumab showed higher incidence of anxiety (12% vs. 8% in patients receiving IFNβ-1a alone), pharyngitis (7% vs 4%), sinus congestion (6% vs. 3%), and peripheral edema (5% vs. 1%) (all $p<0.05$) [3]. Overall, natalizumab's role in the management of MS appears to be one of great value as there are advantages including a tolerable side effect profile, unique mechanism

of action, and a greater level of clinical efficacy in comparison to other disease modifying regimes for MS.

Alemtuzumab

Alemtuzumab (Lemtrada®) is a humanized monoclonal antibody used to treat adults with relapsing forms of multiple sclerosis. Alemtuzumab should be reserved for patients with an inadequate response to at least two drugs indicated for the treatment of multiple sclerosis [6]. Alemtuzumab was originally designed for the treatment of leukemias [7], and eventually a role was found in the treatment of multiple sclerosis. Alemtuzumab works by targeting CD52, an antigen with unknown function, which is expressed on T and B lymphocytes [8]. The employment of Alemtuzumab depletes CD52-bearing B and T cells through antibody-dependent cellular cytolysis and complement-mediated lysis [9]. It is important to note that although Alemtuzumab rapidly depletes T-cells, B-cells, natural killer (NK) cells and monocytes, the repopulation of T and B cells occurs only after the therapy is stopped. The efficacy and safety of alemtuzumab was evaluated in two phase 3 studies, the comparison of Alemtuzumab and Rebif Efficacy in MS (CARE-MS) I and II. All primary outcomes for the treatment of relapsing-remitting MS were reported versus SC IFNβ-1a, not placebo. In CARE-MS I, alemtuzumab reduced the absolute risk reduction by 55% ($p<0.0001$) compared with SC IFNβ-1a. There was a 30% reduction in six-month sustained accumulation of disability, however, statistical significance was not achieved (alemtuzumab, 8% vs SC IFNβ-1a, 11%; $p=0.22$). Side effects seen in CARE-MS I were infections of mild or moderate severity (90% in the alemtuzumab group vs. 45% in the IFNβ-1a group) and thyroid-associated adverse events (by 24 months, 18% in the alemtuzumab group vs. 6% in the IFNβ-1a group) [10]. In CARE-MS II, alemtuzumab reduced the absolute risk reduction by 49% ($p<0.0001$) and six-month sustained accumulation of disability by 42% (alemtuzumab, 13% vs SC IFNβ-1a, 21%; $p=0.0084$) over two years. Side effects seen in CARE MS II were nearly identical to side effects seen in CARE MS I. Infections (77% in the alemtuzumab group vs. 66% in the IFNβ-1a group) and thyroid disorders (16% in the alemtuzumab group) were, as previously shown, associated with alemtuzumab therapy [11].

Mitoxantrone

Mitoxantrone hydrochloride (Novantrone®) is an antineoplastic, immunodulatory agent that is indicated for use in secondary progressive MS (SPMS), in progressive-relapsing MS, and for worsening relapsing-remitting MS. Mitoxantrone, a synthetic anthreacenedione derivative, causes DNA strand-breaks and inter strand cross-links, interferes with DNA and RNA synthesis, and inhibits the enzyme topoisomerase II [12-15]. Mitoxantrone has immunosuppressive activity on T and B lymphocytes and causes apoptosis of B lymphocytes and monocytes [16,17]. One placebo-controlled, double-blind, randomized, multicenter trial evaluated mitoxantrone in progressive multiple sclerosis. The primary efficacy outcome consisted of five clinical measures; change from baseline expanded disability status scale at 24 months, change from baseline ambulation index at 24 months, number of relapses treated with corticosteroids, time to first treated relapse, and change from baseline standardized neurological status at 24 months. Primary outcomes of the trial were as followed: a change in expanded disability status scale (0·24 [0.04-0.44]; $p=0.0194$), change in ambulation index (0.21 [0.02-0.40]; $p=0.0306$), adjusted total number of treated relapses (0.38 [0.18-0.59]; $p=0.0002$), time to first treated relapse (0.44 [0.20-0.69]; $p=0.0004$), and change in standardized neurological status (0.23 [0.03-0.43]; $p=0.0268$). Results showed that Mitoxantrone 12 mg/m [2] was generally well tolerated and reduced progression of disability and clinical exacerbations against placebo, however, potential toxicity should be taken into account [18] (Table 1).

Trial Name and Duration	Treatment Groups	Results
Alemtuzumab CARE-MS I (n=563)19 *Note: CARE-MS I was a rater-blind trial	Alemtuzumab 12 mg daily for 5 days at start of treatment and for 3 days at 12 months (n=376) Interferon beta-1a 44mcg three times per week (n=187) Note: patients enrolled in the study had no prior disease-modifying therapy	At two years, Alemtuzumab significantly reduced the proportion of patients with any relapse (22% vs. 40% for interferon beta-1a, RR 0.45, 95% CI 0.23-0.63) and the annualized relapse rate (0.18 vs. 0.39) There was no significant difference between groups for sustained accumulation of disability (8% vs. 11%)
Alemtuzumab CARE-MS II (n=840)20	Interferon beta-1a 44mcg (n=202) Alemtuzumab 12mg/day (n=426) Alemtuzumab 24mg/day (n=170) Note: patients have previously been treated with at least one MS therapy and experienced relapse	At two years, alemtuzumab significantly reduced the proportion of patients with any relapse (35% vs. 53% for interferon beta-1, RR 0.52, 95% CI 0.39-0.65) and the annualized relapse rate (0.26 vs. 0.52) Unlike CARE-MS I, the alemtuzumab group in CARE-MS II had a significantly lower rate of sustained accumulation of disability (13 vs. 20%, hazard ratio 0.58, 95% CI 0.38-0.87)
Natalizumab AFFIRM (n=942)21	Patients were randomly assigned to receive either Natalizumab 300mg (n=627) or placebo (n=315) every 4 weeks and have experience at least one relapse in the preceding year.	Patients receiving Natalizumab were found to have a relapse rate of 25% per patient year when compared to a relapse rate of 74% in the placebo group
Natalizumab SENTINEL (n=1171)22	Patients were randomly assigned to receive either Natalizumab 300mg (n=589) or placebo (n=582) as well as interferon beta-1a 30mcg. Patients had previously experienced a relapse despite previous treatment with interferon	Patients receiving Natalizumab were found to have a relapse rate of 36% per patient year compared with a relapse rate or 78% per patient year in the placebo group.

Table 1: Clinical Trials for Alemtuzumab and Natalizumab in Relapsing-Remitting Multiple Sclerosis (RRMS)

Conclusion

Infusion therapy with the use of Alemtuzumab and Natalizumab are the mainstay of treatment for patients with RRMS. Although no head-head trials have directly compared these two agents, infusion therapy with Natalizumab is the drug of choice in those patients who value effectiveness above safety and convenience [19,20]. The justification for the use of these agents are based upon cross-trial comparisons and clinical experience however their superior efficacy over other disease modifying therapies for RRMS cannot be defined confidently. We have reviewed the literature surrounding the use of these infusion therapies and have proven their efficacy through the reduction in annualized relapse rate in RRMS. Both Natalizumab and Alemtuzumab have revolutionized the treatment approach to RRMS and have lessened the clinical burden in those patients affected by this debilitating auto-immune disease [21].

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