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REVIEW

Review of daclizumab and its therapeutic potential in the treatment of relapsing–remitting multiple sclerosis

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Jennifer Reardon[1]
Jai S Perumal[1,2]

[1]Weill Cornell MS Center at Nyack Hospital, Nyack Hospital, Nyack, NY, USA; [2]Department of Neurology, Weill Cornell Medical College, New York, NY, USA

Abstract: Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system. It can present in several forms, with the relapsing–remitting pattern being the most common. Since the approval of the first disease-modifying therapy and the initiation of appropriate treatments from the early stages of the disease, there seem to be positive impacts on the long-term outcomes and disability associated with MS. Currently, there are ten approved drugs for the treatment of MS, and several more are in various stages of development. These medications each have their unique profile in terms of efficacy, dose, routes of administration, tolerability, and adverse effects. Daclizumab is a humanized monoclonal antibody that is being explored for the treatment of MS. It is currently approved for use in allograft renal transplantation. Given its modulatory effects on the immune system, daclizumab's potential for use in MS was tested in extensive Phase II trials. With continued demonstration of its efficacy, it is currently in a Phase III trial for relapsing–remitting MS. While daclizumab has demonstrated beneficial effects in controlling disease activity in MS, there were also some safety and tolerability concerns that were raised. Further information from the ongoing Phase III trial, and from open-label studies, will shed light on the benefit and risk profile of this drug and its potential for use in MS.

Keywords: multiple sclerosis, disease-modifying therapy, monoclonal antibodies, daclizumab, clinical trials

Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS). Though the exact cause of MS has not been discovered, it is believed that in a genetically predisposed individual, some environmental trigger leads to the onset of the disease.[1] MS can present in several forms, with the relapsing–remitting pattern being the most common. Prior to the approval of the first disease-modifying therapy for MS in 1993, there were no medications proven to alter the disease course. With the advent of medications and the initiation of appropriate treatments from the early stages of the disease, there seem to be positive impacts in terms of the long-term outcomes and disability in MS. Currently, there are ten US Food and Drug Administration (FDA)-approved drugs for the treatment of MS, and several more are in various stages of development, as shown in Table 1.[2] These medications each have their own unique profile in terms of efficacy, dose, routes of administration, tolerability, and adverse effects. The earliest approved treatments are all injectable therapies and include the various formulations of the interferon beta and glatiramer acetate.[3–6] Natalizumab and mitoxantrone are infusion therapies that appear to have greater efficacy compared to the injectable therapies.[7–9] More recently, over the course of the last 3 years, three

Correspondence: Jai S Perumal
Weill Cornell Medical College,
1305 York Ave, 2nd floor,
New York, NY, USA 10021
Tel +1 646 962 5733
Fax +1 646 962 0390
Email jsp9007@med.cornell.edu

Table 1 FDA-approved therapies and treatments in Phase III trials for MS

Disease-modifying agent	Dose, route, and frequency of administration	Year of FDA approval	Adverse effects
Interferon beta-1b (Betaseron®; Bayer HealthCare Pharmaceuticals, Montville, NJ, USA)	0.25 mcg SC, every other day	1993	Flu-like symptoms; leukopenia; elevated liver enzymes; thyroid dysfunction
Interferon β-1a (Avonex®; Biogen Idec, Inc, Weston, MA, USA)	30 mcg IM, once per week	1996	Flu-like symptoms; leukopenia; elevated liver enzymes; thyroid dysfunction
Glatiramer acetate (Copaxone®; Teva Pharmaceutical Industries, Ltd, Petah Tikva, Israel)	20 mg SC, daily	1997	Injection-site reactions; lipoatrophy; postinjection vasomotor syndrome
Mitoxantrone (Novantrone®; EMD Serono, Inc, Rockland, MA, USA)	Variable based on BSA	2002	Infections; bone marrow suppression; nausea, hair thinning; bladder infections; mouth sores
Interferon beta-1a (Rebif®; Merck KGaA, Darmstadt, Germany)	44 mcg SC, three times per week	2002	Flu-like symptoms; leukopenia; elevated liver enzymes; thyroid dysfunction
Natalizumab Tysabri® (Biogen Idic, Inc, Weston, MA, USA)	300 mg IV, every 4 weeks	2006	Hypersensitivity reactions; infusion reactions (headache, rigors); PML risk; infection risk
Interferon beta-1b (Extavia®; Novartis International AG, Basel, Switzerland)	0.25 mcg SC, every other day	2009	Flu-like symptoms; leukopenia; elevated liver enzymes; thyroid dysfunction
Fingolimod (Gilenya®; Novartis International AG)	0.5 mg oral, daily	2010	Headache; elevated liver enzymes; cough; lymphopenia; infections; bradycardia
Teriflunomide (Aubagio®; Genzyme Corporation, Cambridge, MA, USA)	7 mg and 14 mg oral, once daily	2012	Abnormal liver function; alopecia; nausea; teratogenic
BG-12 (Tecfidera™; Biogen Idec, Inc)	240 mg oral, twice per day	2013	Flushing; abdominal pain; nausea; diarrhea
Alemtuzmab (Lemtrada™; Genzyme Corporation)	12 mg IV, 5 consecutive days initially, then 3 consecutive days annually	Under FDA review	Risk of infections; infusion reactions; secondary autoimmune disorders including thyroid diseases and idiopathic thrombocytopenic purpura
Ocrelizumab	600 mg and 1,000 mg IV doses used in clinical trials, cycles of two doses, 2 weeks apart every 6 months	Phase III trials	Mild to moderate infusion reactions; risk of infections
Daclizumab	150 mg and 300 mg SC in clinical trials, every 4 weeks	Phase III trials	Risk of infections; secondary autoimmune disorders; cutaneous events; elevated liver enzymes
Laquinimod	0.6 mg and 1.2 mg daily, administered orally	Phase III trial	Elevated liver enzymes; abdominal pain

Abbreviations: FDA, US Food and Drug Administration; MS, multiple sclerosis; SC, subcutaneous; IM, intramuscularly; BSA, body surface area; IV, intravenous; PML, progressive multifocal leukoencephalopathy.

oral agents namely Fingolimod, Teriflunomiide and Dimethyl Fumarate (BG-12) were added to our armamentarium.[10–15] Laquinimod is another oral agent that is being further studied for its use in MS. Laquinimod had completed two Phase III clinical trials, but did not meet its primary endpoint in one of these studies and is currently undergoing a third Phase III trial for relapsing–remitting MS (RRMS).[16,17] Given the multiple treatment options that are available now, and given the agents that are currently in development, it is an exciting time for patients with MS and the clinicians involved in their care, as the arsenal against MS has continued to expand.

Monoclonal antibodies are an exciting class of medications with immense therapeutic opportunity for MS; the first in its class to be approved for the treatment of MS was natalizumab.[7,8] Natalizumab is a humanized monoclonal antibody against α4β1 and α4β7 integrins, which acts by preventing lymphocyte egress across the blood–brain barrier, and which can access the CNS.[18,19] Rituximab is an anti-CD20 monoclonal antibody that has been studied in MS and has demonstrated clinical efficacy.[20] It is approved for the treatment of several other autoimmune disorders, but currently there are no ongoing studies of its use in MS. However, ocrelizumab,

which is a humanized form of the anti-CD20 antibody, is in Phase III trials for RRMS and primary progressive MS as well. Alemtuzumab is a humanized anti-CD52 monoclonal antibody, currently FDA-approved for the treatment of chronic lymphoid leukemia. Phase II and Phase III studies in relapsing MS have shown superior efficacy compared with interferon beta therapy, and alemtuzumab is currently under FDA review for its MS indication.[21,22]

Daclizumab is a humanized monoclonal antibody that is being explored for the treatment of MS. It is currently approved for use in allograft renal transplantation.[23,24] Given its modulatory effects on the immune system, daclizumab's potential for use in MS was tested, and after promising results from initial studies, several Phase II studies were undertaken.[25,26] After daclizumab continued to demonstrate efficacy without posing significant risks in quite extensive Phase II trials, it is currently in a Phase III trial for RRMS.

Mechanism of action

Daclizumab is a humanized monoclonal antibody directed against the α subunit (CD25 or Tac) of the interleukin (IL)-2 receptor. It is a competitive inhibitor of the IL-2 receptor, which presents predominantly on activated lymphocytes. Through binding of the high-affinity IL-2 receptor, the mechanism of action (MOA) of daclizumab was believed to be the inhibition of the activation of lymphocytes.[27,28] Several studies have established that IL-2 is a potent activator of lymphocytes, and blocking of this receptor results in amelioration of inflammation.[29] In vitro experiments demonstrated that specific binding of daclizumab to IL-2α resulted in the inhibition of T-cell proliferation in response to antigenic stimuli.[30–32] However, contrary to these findings, in vivo studies in MS patients treated with daclizumab showed normal T-cell activation and proliferation, suggesting that immune mechanisms are involved in overcoming this blockade take effect, which enable T-cell activation and proliferation to occur; in addition, the clinical effects of daclizumab may not result from the direct inhibition of T-cell proliferation.[33,34] At present, it appears that daclizumab affects several immune processes, and the full extent of its MOA is complex.[35]

The effect of daclizumab on natural killer (NK) cells has been of particular interest.[36] It has been shown that daclizumab therapy results in selective expansion of a subset of NK cells labeled CD56^{bright} NK cells.[33] There is evidence from prior studies in pregnancy that CD56^{bright} NK cells appear to play a role in the immune tolerance of the mother to the fetus.[37–39] Since the discovery of the expansion of CD56^{bright} NK cells in MS patients treated with daclizumab, further studies examining the mechanism by which these cells exert their anti-inflammatory effects have demonstrated that CD56^{bright} NK cells are involved in killing activated T-cells, which could explain some of the anti-inflammatory effects of daclizumab.[40] Another potential MOA of daclizumab is the inhibition of T-cell activation by mature dendritic cells.[41,42] It has also been hypothesized that yet another possible action of daclizumab is the inhibition of inflammatory effects of innate lymphoid cells.[43,44] Thus, at present, the MOA of daclizumab seems to involve multiple aspects of the immune system.

Clinical trial data

Several studies have examined the potential of daclizumab as a disease-modifying therapy for MS.[45,46] After the efficacy of daclizumab was reported in earlier smaller Phase II trials, larger Phase II trials were undertaken.[47,48]

The CHOICE study[47] was a Phase II, double-blind, placebo controlled trial that evaluated daclizumab in combination with interferon beta in active relapsing MS patients. Two hundred and thirty patients with relapsing MS who were on interferon beta therapy were randomized in a 1:1:1 manner to receive daclizumab therapy at high doses, daclizumab at low doses, or placebo in addition to continuing their interferon regimen. Thus, the trial consisted of three treatment arms: (1) interferon beta plus high-dose daclizumab (2 mg/kg) every 2 weeks; (2) interferon beta plus low-dose daclizumab (1 mg/kg) every 4 weeks; and (3) the interferon beta plus placebo arm. The duration of the study was 24 weeks. The primary endpoint was the total number of new or enlarged gadolinium-enhancing lesions measured on magnetic resonance imaging (MRI) of the brain performed every 4 weeks between week 8 and week 24. Among several secondary endpoints was the annualized relapse rate (ARR). The adjusted mean number of new or enlarged gadolinium contrast-enhancing lesions in the high-dose daclizumab plus interferon beta group was 1.32 versus 4.75 in the interferon beta and placebo group (a difference of 72%; 95% confidence interval [CI]: 34%–88%; $P = 0.004$). For the low-dose daclizumab plus interferon beta group, the number of new or enlarging gadolinium-enhancing lesions was 3.58 (a difference of 25%; 95% CI −76% to 68%; $P = 0.51$). Among the secondary endpoints evaluated was the ARR. The unadjusted ARR was 0.86 in the interferon beta and placebo group; 0.49 in the high-dose daclizumab and interferon beta group (a difference of 43%; 95% CI −28% to 74%; $P = 0.18$); and 0.58 in the low-dose daclizumab and interferon beta group (a difference of 32%, 95%; CI −45% to 69%; $P = 0.31$). The results indicated that the group with high-dose daclizumab

and interferon beta therapy had a statistically significant reduction in new or enlarging gadolinium-enhancing lesions when compared to the interferon beta and placebo group.

After results from earlier studies established the potential benefit of daclizumab in combination with interferon beta over that of interferon beta alone in reducing disease activity in relapsing MS, another Phase II trial – the SELECT study[48] – was undertaken, which evaluated daclizumab as a monotherapy in RRMS. The daclizumab high-yield process (HYP) – which has an identical amino acid sequence as daclizumab, but differs in terms of its glycosylation process and gives rise to fewer antibody-dependent instances of cytotoxicity – was tested in the trial. Six hundred and twenty-one patients with RRMS were randomized in a 1:1:1 manner to receive daclizumab HYP 150 mg subcutaneous injections every 4 weeks, or daclizumab HYP 300 mg subcutaneous injections every 4 weeks, or placebo for 52 weeks. The primary endpoint of the study was the ARR at week 52. The ARR with daclizumab HYP 150 mg was 0.21, a 54% reduction as compared to placebo (95% CI: 33%–68%; $P < 0.0001$); the ARR with daclizumab HYP 300 mg was 0.23, a 50% reduction compared to placebo (95% CI: 28%–65%; $P = 0.0003$); and the ARR for the placebo group was 0.46. The proportion of patients who remained relapse-free during the study was higher for both of the daclizumab HYP-treated groups than for the placebo group. The numbers were 81% ($P < 0.0001$) for the daclizumab HYP 150 mg group, 80% ($P = 0.0003$) for the daclizumab HYP 300 mg group, and 64% for the placebo group. The daclizumab HYP groups also demonstrated superiority compared to placebo on MRI outcomes, including on new gadolinium-enhancing lesions and on new or enlarging T2 lesions. There was a beneficial impact on disability progression as well in the daclizumab HYP-treated groups versus placebo, with the daclizumab HYP 150 mg dose demonstrating a 57% reduction at week 52 compared to placebo, and the daclizumab HYP 300 mg dose exhibiting a 43% reduction at week 52 compared to placebo.

The SELECTION study is an open-label extension of the Phase II SELECT trial.[49] The goal of this study was to evaluate the long-term safety, efficacy, and immunogenicity of daclizumab HYP monotherapy in subjects with RRMS. In this study, subjects who completed the SELECT study were provided with an option to receive daclizumab HYP monotherapy for 144 weeks. Preliminary results from this trial were presented at the European Committee for Treatment and Rehabilitation in Multiple Sclerosis (ECTRIMS) meeting in Lyons, France in October 2012.[50] The trial demonstrated sustained efficacy in subjects continuing on daclizumab HYP for 2 years, with an ARR of 0.17 in year 2 (0.15 in year 1), and the occurrence of new T2 lesions were 1.2 in year 2 and 1.9 in year 1.

Safety and tolerability

In the CHOICE study,[47] the incidence of common adverse events was similar in all the treatment groups. There were no life-threatening or opportunistic infections. The incidence of cutaneous events was higher in the daclizumab groups when compared to the interferon beta plus placebo group (24% versus 6%). There were two malignancies reported in the daclizumab-treated groups. One patient with a family history of breast cancer developed ductal carcinoma in situ more than 1 year from her last daclizumab dose, and another patient had a recurrence of preexisting pseudomyxoma peritonei. In the SELECT trial,[48] nine patients (2%) in the daclizumab HYP groups were reported to have serious infections, as opposed to none in the placebo group. Seven of these occurred while on daclizumab HYP treatment. One patient discontinued treatment permanently due to the infection, while the others resumed daclizumab HYP treatment after resolution of the infection. As was previously seen in the CHOICE study,[47] there were more cutaneous events in the daclizumab HPY groups. The incidence in the daclizumab HYP 150 mg group was 18%, while in the daclizumab HYP 300 mg group, the incidence was 22%, and in placebo group it was 13%.[48] Among these, five patients in the daclizumab HYP groups were designated as having serious cutaneous events, which consisted of a case of rash, atopic dermatitis, allergic dermatitis, exfoliative dermatitis, and erythema nodosum, respectively. There was one case each of autoimmune thyroiditis, Crohn's disease, hypersensitivity, and lymphadenopathy in the daclizumab HYP 300 mg group, and this was compared to the placebo group, which exhibited no similar cases. There were four malignancies reported in the trial: two cases of cervical carcinoma (one in the placebo group and one in the daclizumab HYP group), and two cases of melanoma in the daclizumab HYP groups. There was one death in the daclizumab HYP 150 mg group; the patient developed a serious rash and subsequently died of complications from an undiagnosed psoas abscess. Autopsy revealed a mesenteric artery thrombosis adjacent to the abscess, as well as ischemic colitis. Liver enzyme abnormalities were similar in all three groups, but the daclizumab HYP-treated groups had a higher number of these abnormalities, with elevations greater than five times the upper limit of normal (4% in both daclizumab HYP-treated groups versus 1% in the placebo group).

In addition to what was reported in the Phase II clinical trials, there was a recent case report of a woman who developed CNS vasculitis while on daclizumab therapy.[51] The patient had participated in a Phase II trial of daclizumab and elected to continue daclizumab therapy after completion of the trial in an off-label manner. She had received a total of 21 doses of daclizumab prior to the onset of symptoms of CNS vasculitis. In the preliminary results from the SELECTION study,[50] which was an open label extension of the SELECT trial,[48] the side effect profile was similar; however, there was one death reported from autoimmune hepatitis in the SELECTION study.[50]

With regard to pregnancy and breastfeeding, daclizumab (Zenapex®; F Hoffman-La Roche Ltd, Basel Switzerland) is designated as pregnancy category C, and the FDA recommends that nursing mothers discontinue the medication as there are not enough data regarding its excretion in breast milk and its potential harmful effects.

Further studies

The DECIDE study – which is a Phase III multicenter, double-blind, randomized trial where daclizumab HYP is administered at a dose of 150 mg once every 4 weeks versus interferon beta-1a, which is administered once weekly for 96 to 144 weeks in RRMS patients – is currently ongoing. The primary endpoint of this study is the ARR. Several secondary endpoints including functional disease progression and quality of life are being evaluated as well.[52]

Conclusion

MS is a complex immune disorder – the exact etiology of which is still not understood. The disease patterns in MS are widely variable, with some patients having a relatively milder disease course, even years after the onset of the disease, while others accrue significant early disability. Given the multiple potential disease mechanisms and the wide spectrum of the disease, one drug is unlikely to be a universal fit for all patients. Even though perfect biomarkers that predict the subsequent disease course of MS have not been discovered, based on the data from natural history studies and treatment trials, one could potentially use a patient's early disease characteristics (both clinical characteristics and MRI parameters) to help understand the nature of that particular individual's long-term disease course when deciding an appropriate treatment regimen. The growing armamentarium of therapies for treating MS provides us with more options when choosing optimal therapy, and takes us a step closer to personalized medicine and finding the best fit for each patient based on the patient's disease characteristics and the benefit/risk profile for a specific drug.

Among the currently available therapies, the injectable medications have a well-established safety profile, but they are partially effective and have tolerability and adherence issues due to their parenteral route of administration and their side effects. The currently available monoclonal antibody, natalizumab, appears to have greater efficacy and patients appear to experience greater quality of life when compared to patients using injection therapies. However, natalizumab has the potential risk of progressive multifocal leukoencephalopathy, especially in individuals who test positive for the JC virus antibody with prolonged natalizumab use. The oral agents offer ease of administration but have their own individual risks and tolerability concerns. Fingolimod has the risk of infections including herpes infections and potential cardiac concerns, among others. Teriflunomide has a rating of pregnancy category X. In its clinical trials, BG-12 did not appear to demonstrate any major concerns with infections or metabolic abnormalities; however, there were some tolerability issues, especially at the commencement of treatment, and as with all new medications, there is the lack of data with long-term use.

Daclizumab has demonstrated efficacy on several clinical parameters including relapse rate, disability progression, and on MRI markers of disease activity as well (including gadolinium-enhancing lesions and T2 lesions). However, some safety concerns were raised, including the risk of cutaneous events, elevated liver enzymes, infections, and secondary autoimmune disorders. Further information from its ongoing Phase III trial and open-label studies will shed light on the benefit/risk profile of this drug. There is also ongoing research into the identification of potential biomarkers, which might help determine an individual's likelihood of responding to daclizumab, and it may also help establish the probability that a patient is at risk of experiencing adverse events with treatment initiation. If daclizumab treatment could be associated with potential serious adverse events, then when considering daclizumab as a disease-modifying therapy for MS, one would need to examine its efficacy in comparison to alternate treatments that might be used in a similar circumstance. Treatments that one could consider in this scenario would include natalizumab and fingolimod (which are currently available for the treatment of MS), alemtuzumab (which is under FDA review and expected to be available soon), and ocrelizumab (which is undergoing Phase III trials). Ultimately, the results from ongoing Phase III trials and observation studies will determine daclizumab's place in the treatment of MS.

Disclosure

Jennifer Reardon is a speaker for Biogen Idec and Teva Pharmaceuticals. Jai S Perumal is a speaker and consultant for Biogen Idec, Teva Pharmaceuticals, and Genzyme. The authors report no other conflicts of interest in this work.

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