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REVIEW

# Anti-CD25 (daclizumab) monoclonal antibody therapy in relapsing–remitting multiple sclerosis

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**Abstract** Following the recent approval of the first oral therapy for multiple sclerosis (MS), fingolimod, multiple other oral compounds, and also a number of monoclonal antibodies (mab) are currently in phase III clinical testing. One of these is daclizumab, a humanized mab against the interleukin-2 receptor alpha chain (IL2RA or CD25). Efficacy to block clinical and inflammatory activity of relapsing–remitting MS (RR-MS) has been shown for daclizumab in several small phase IIa studies and one large phase IIb clinical trial, and phase III testing is ongoing. Different from prior expectations about its mechanism of action that anticipated that daclizumab would block the activation and expansion of autoreactive T cells, we and others have shown that the expansion of regulatory natural killer (NK) cells, which express high levels of the marker CD56, appears to be the most important biological effect of CD25 blockade. From these data CD25 inhibition is one of the most promising upcoming treatments of RR-MS and possibly also other autoimmune conditions. Clinical and mechanistic data will be summarized in this short review.


**Contents**



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## 1. Introduction

All available treatments for MS and most of those in mid- to late stage clinical development are either immunosuppressive or immunomodulatory. These include interferon-b (IFN-$\beta$) and glatiramer-acetate (GA), which have been approved over a decade ago and remain the main first-line treatments of RR-MS, a humanized monoclonal antibody against CD49d/very late antigen-4 (VLA-4), natalizumab, which is substantially more effective than IFN-$\beta$ and GA, and the recently introduced fingolimod, a sphingosin-1 phosphate receptor agonist, the first oral therapy of RR-MS. Mitoxantron, a chemotherapeutic drug, has been approved for both RR-MS and secondary progressive MS (SP-MS) with ongoing relapse activity, and finally azathioprine, another immunosuppressive compound which has been on the market for several decades, however for other indications than MS, has also been approved for MS in some countries. Cladribine, a potent immunosuppressive and orally available compound, has recently also been approved in a few countries, but marketing has been stopped after approval had been denied in North America and Europe. Besides these already approved drugs, several other small molecule drugs or monoclonal antibodies are in late stage clinical development and these include the orally available compounds fumaric acid, teriflunomide and laquinimod [1], and finally the mabs alemtuzumab (humanized anti-CD52), rituximab/ocrelizumab (chimeric- and humanized anti-CD20 respectively) and daclizumab (humanized anti-CD25) [2]. A chimeric anti-CD25 mab, basiliximab, like daclizumab has long been approved for the prevention of allograft rejection; however, it has not been tested as a treatment of MS in a clinical trial thus far. Daclizumab (Zenapax®) has recently been withdrawn from the market. While the reasons for this withdrawal are not clear, the decision was most likely based on strategic/marketing considerations and not related to the safety profile or other characteristics of daclizumab.

The latter anti-CD25 mab daclizumab, which shall be briefly reviewed here, was originally developed by Thomas Waldmann, National Cancer Institute, National Institutes of Health (NIH), Bethesda, to block cell proliferation of virally transformed T cells in human T lymphotropic virus I (HTLV-I)-induced adult T cell leukemia (ATL) [3,4]. Daclizumab is the humanized version of the initial mouse mab, which is directed against the interleukin-2 receptor alpha chain (IL2RA, CD25). Daclizumab is an IgG1 mab and binds to the TAC epitope or binding site of IL-2 to CD25. Different from numerous other cell-depleting mabs, e.g. rituximab/ocrelizumab and alemtuzumab, daclizumab binds to the CD25 epitope and "masks" the IL-2 binding site, but does not lead to complement fixation, antibody-mediated cellular cytotoxicity, relevant modulation of the CD25 molecule or the entire IL-2 receptor complex, and also does not induce signaling events or has agonistic activities [2]. As mentioned previously, daclizumab had been approved under the name Zenapax® for many years as an immunomodulatory/-suppressive treatment for the prevention of allograft rejection and for treating ATL.

With respect to clinical use outside of transplantation medicine and oncology (in ATL), daclizumab has been tested successfully in cases of treatment-refractory uveitis by Nussenblatt, Waldmann and colleagues at the National Eye Institute, NIH [5], and later also in HTLV-I-associated myelopathy/tropical spastical paraparesis (HAM/TSP), a HTLV-I-induced and at least in part immune-mediated chronic encephaloymelitis, by Jacobson, Waldmann and colleagues [6]. In these exploratory trials the rationale was to block the expansion or virus-specific (HAM/TSP) and/or autoreactive (uveitis and possibly also in HAM/TSP) T cells after their activation and hence also the subsequent steps, which presumably lead to tissue damage in the central nervous system (CNS) in HAM/TSP or the eye in uveitis. Particularly in the uveitis trials, anti-CD25 treatment looked promising with respect to halting disease activity in patients, in whom the autoimmune disease could not be controlled by other medications, but there was also an indication of efficacy in HAM/TSP, and in both indications no serious safety concerns arose [5–8]. Following the positive experience and favorable safety profile of anti-CD25 treatment in uveitis and HAM/TSP, we (the Cellular Immunology Section, NINDS, NIH; R. Martin and colleagues) and the Department of Neurology, University of Utah at Salt Lake City (J. Rose and colleagues) began to explore the use of anti-CD25/daclizumab also in RR-MS patients with active inflammation RR-MS.

## 2. Clinical Observations

Until now, six clinical trials have been conducted with daclizumab all in RR-MS and SP-MS (the manuscript from the last phase IIa trial in treatment-naive RR-MS at NINDS is in preparation), and the main results of the five published trials will be summarized briefly here (see also Table 1). The first two trials were single center trials conducted at NINDS, NIH, as a baseline-to-treatment crossover and MRI-controlled phase IIa study in RR-MS and SP-MS patients, who had failed IFN-$\beta$ therapy [9], and an open proof-of-concept study at the University of Utah, Salt Lake City, by Rose and colleagues, which included both RR- and SP-MS patients, who had failed single or multiple treatments prior to enrollment [10]. In the meantime, three other phase IIa trials and one larger phase IIb study with intravenous daclizumab (once monthly) have been conducted including two more baseline-to-treatment crossover studies either in IFN-$\beta$ non-responders [11,12] or treatment-naive RR-MS patients (manuscript in preparation) and the placebo-controlled, randomized multicenter phase IIb trials (CHOICE trial), in which two doses of subcutaneous (s.c.) daclizumab were compared against placebo [13]. Below, the main results of these trials will be summarized in chronology of initiation and/or publication.

NINDS daclizumab trial 1 [9]: The target population was RR-MS patients, who had failed IFN-$\beta$. In this baseline-to-treatment crossover, MRI-controlled study, the reduction of gadolinium (Gd) contrast-enhancing, i.e. fresh inflammatory lesions served as the primary outcome, and additional clinical, MRI and laboratory parameters were followed as well. The most important entry criteria was the requirement of continuing MRI activity (Gd+lesions) during the baseline phase and while the patients were still treated with IFN-$\beta$. When fulfilling this activity criterion, patients were enrolled after four monthly baseline MRIs and daclizumab (1 mg/kg body weight, every 4 weeks i.v.; first two doses given at two weekly intervals and then monthly) was added to the