

Daclizumab Phase III Trial in Relapsing and Remitting MS: MRI and Clinical Results

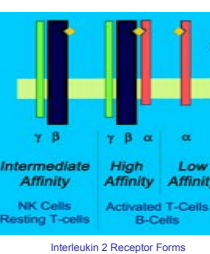
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Abstract

Objective: A trial of Daclizumab in patients with relapsing and remitting multiple sclerosis (MS) was performed to determine effects on MRI and clinical parameters.
Background: Daclizumab is a humanized monoclonal antibody specific for the Interleukin 2 receptor chain that has shown promising effects in the treatment of MS.
Methods: MS patients on interferon therapy but with continuing relapses and contrast enhancing lesions (CEL) were selected for participation. Patients were evaluated with serial monthly MRI scans and clinical rating scales including Timed Ambulation, EDSS and NRS from 3 months prior to Treatment (baseline) and then at 0.5 months to 27.5 months during treatment. Daclizumab (1mg/Kg IV) was initiated at baseline and administered again in 2 weeks followed by every 4 week treatments according to a protocol developed at NIH and approved by the University of Utah IRB. Interferon was continued until 5.5 months after Daclizumab was initiated. Patients without continuing CEL were placed on Daclizumab monotherapy and patients with recurrent CEL were continued on interferon with Daclizumab therapy at (1.5mg/Kg IV) every 28 days per protocol. The primary outcome measure was the number of total and new CEL with clinical scores as secondary measures.
Results: Eight patients qualified for treatment with Daclizumab. One patient developed a severe relapse prior to Daclizumab initiation and therapy was discontinued after two treatments. Seven patients continued on treatment. Two patients were observed to have recurrent new CEL and restarted interferon in addition to an increase in Daclizumab dose. Total CEL and new CEL were compared between pretreatment scans subsequent scans in 3-month intervals. Significant four fold reductions in total CEL (p<0.05 to 0.001) and new CEL (p<0.001) were observed at all seven intervals after treatment initiation. Significant reductions in Timed Ambulation, EDSS and NRS were observed. Treatment resulted in a significant decrease in the number of relapses (p<0.001).
Interpretation: Daclizumab appears to be effective in reducing CEL and in improving clinical scores in relapsing-remitting MS patients with active disease not controlled by interferon alone. Optimal therapy for some patients may require combination treatment with interferon. These results promise efficacy and support further clinical development of daclizumab in patients with active relapsing and remitting MS.

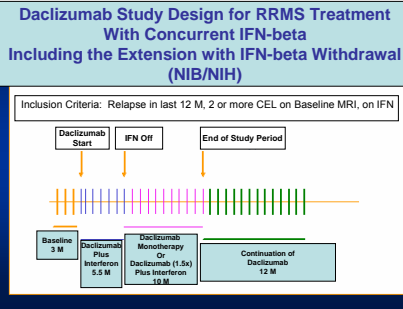
Introduction



Multiple sclerosis is an inflammatory demyelinating disease of the CNS which partially responds to immune based therapies (1,2). Patients that do not respond to the currently approved treatments continue to have relapses and gadolinium enhancing lesions on MRI scans. A new direction in therapy would be advantageous for this patient population. The interleukin 2 receptor (IL2R) involved in activation of T and B cells is a potential target for immunologic therapy (3,4). Previous experiments in EAE have shown that IL2R directed immunotherapies can ameliorate this model disease (5-7). A humanized monoclonal antibody, Daclizumab, binds to the alpha chain (CD25) of the IL2R and therefore binds to the high affinity but not the intermediate affinity receptor.

Daclizumab is FDA approved for prevention of renal allograft rejection(8). The antibody has been utilized to treat autoimmune diseases including non-infectious uveitis and multiple sclerosis (9-11). In the present investigation a phase III study was designed based on a protocol designed by Dr. Roland Martin and colleagues in the Neuroimmunology Branch at NIH. Daclizumab administration over 27.5 months and the potential for monotherapy are evaluated in this small phase III trial.

Daclizumab Properties
 Humanized IgG1 antibody
 Specific to IL2R α chain (CD25)
Pharmacokinetic
 T_{1/2} 20 Days
 Range of T_{1/2} 11-30 Days



Inclusion Criteria:
 1)Diagnosis of primary progressive MS, defined as gradual progression of disability from the onset without relapses.
 2)Abnormal screening/pre-treatment blood tests exceeding any of the limits defined in the protocol.
 3)Concurrent, clinically significant (as determined by the investigator) cardiac, immunologic, pulmonary, neurologic, renal, and/or other major disease.
 4)Any contraindication to monoclonal antibody therapies.
 5)If prior treatment was received, the subject must have been off treatment for the required period prior to enrollment. Glatiramer Acetate or Cytoxan 26 weeks, all other immunosuppressive therapies and plasma exchange 12 weeks except for corticosteroids and ACTH 8 weeks
 6)Prior treatment with any other investigational drug or procedure for MS.
 7)History of alcohol or drug abuse within the 5 years prior to enrollment.
 8)Female subjects not practicing adequate contraception.
 9)Unwillingness or inability to comply with the requirements of this protocol including the presence of any condition (physical, mental, or social) that is likely to affect the subject's retention for follow-up visits on schedule.
 10)Pregnancy or Breastfeeding

Exclusion Criteria:

Treatment Protocol and Outcome Measures:
 An NIH Daclizumab Treatment Protocol developed by Dr. Roland Martin and colleagues* was adapted to this investigation. The protocol is detailed in the Figure Above. The specific treatment regimen is explained below:
 All patients that qualified by the inclusion criteria and have presence of 2 or more Gd-contrast enhancing MRI lesions (CELS) on one or more of four baseline MRIs entered the treatment phase of the study. The initial therapy was Daclizumab 1mg/kg initially and in two weeks followed by the same dose every four weeks for a total of 5.5 months of treatment with concomitant interferon therapy. If the patient had cessation of CELs during the initial treatment phase then the interferon was discontinued and daclizumab monotherapy at 1mg/kg every 4 weeks was continued for an additional 10 months. If CELs were not suppressed during the initial phase then interferon therapy was continued and the dosage of daclizumab was increased to 1.5mg/kg. If after cessation of interferon CELs returned then patients were also increased to 1.5mg/kg and interferon therapy was reinstated. The treatment protocol concluded at 15.5 months with an extension phase for the additional 12 months.

Primary Outcome: Mean number of new and total contrast enhancing lesions (CEL) 3mm or greater.
Secondary Outcome: Clinical outcome measures (Relapses, EDSS, NRS and Timed Ambulation).
Statistics: MRI and clinical measures were analyzed using GraphPad Instat statistical software (GraphPad Software Inc. San Diego, CA, USA). For multiple comparisons, ANOVA, Tukey-Kramer multiple comparisons test was performed for total CEL, new CEL, timed ambulation and relapses. Multiple comparisons for EDSS and NRS were performed with Kruskal-Wallis test, non parametric ANOVA.

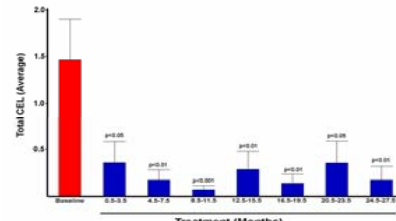
Methods

Results

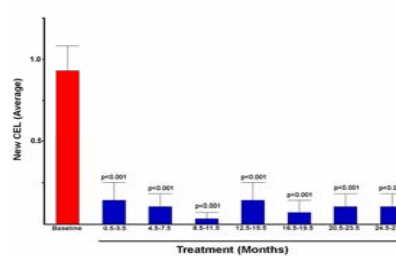
Enrollment: Eighteen Patients were screened with baseline scans and Eight patients qualified for treatment with Daclizumab. One patient developed a urinary tract infections followed by a severe relapse at the time of Daclizumab initiation and therapy was discontinued after two treatments. Seven patients continued in the study and completed the 27.5 months of the daclizumab treatment. Two patients were observed to have recurrent new CEL and restarted interferon in addition to an increase in Daclizumab dose.
Primary Outcome: The total CEL and new CEL were compared between pretreatment scans subsequent scans in 3-month intervals. A significant reduction in total CEL was observed in the treatment intervals (p<0.05 to p<0.001). New CEL were reduced four-fold at all seven intervals after treatment initiation (p<0.001).
Secondary Outcome: Significant reductions in EDSS, NRS and Timed Ambulation were observed. Overall, daclizumab therapy resulted in a significant decrease in the number of relapses (p<0.001).
Side effect Profile: During the 27.5 months treatment phase of the study 197 infusions of daclizumab were administered. The medication was generally well tolerated. Side effects included: rash in 2 patients and post-treatment febrile reaction in 1 patient; these side effects did not preclude therapy. In one patient lymphadenopathy developed at 25.5 months. The lymphadenopathy fluctuated and persisted in the next two months. Lymph node biopsy revealed a nonspecific reactive change. The patient also had two upper respiratory tract infections during this time, developed fever with an infiltrate on chest X-ray and was diagnosed with a pneumonia requiring outpatient antibiotic therapy. After completion of the protocol the lymphadenopathy receded.

MRI Results

Total CEL

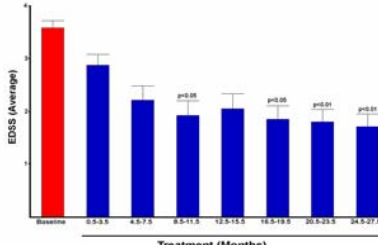


New CEL

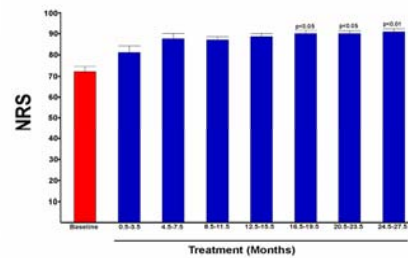


Clinical Results

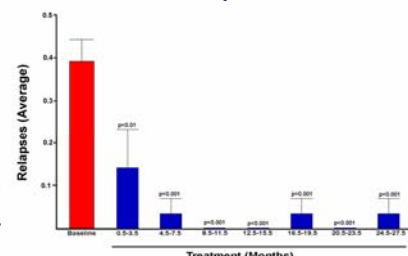
EDSS



NRS



Relapses

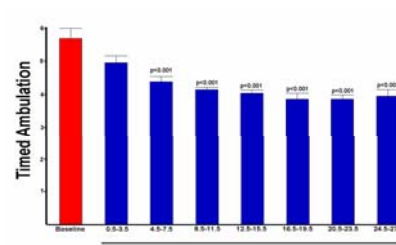


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Discussion

Timed Ambulation



Conclusions

Daclizumab is a promising new therapy for immune mediated disorders including MS. A previous study by Glebovskaya et al. demonstrated significant reduction in total and new CEL in a short term study of daclizumab in combination with interferon (10). Our open-label case series suggested a potential for monotherapy (11). To further evaluate daclizumab we initiated the present phase III trial in parallel with a similar investigation by our colleagues at NIH in order to evaluate efficacy of the antibody over a longer term of administration and to determine if monotherapy could be effective. We have demonstrated significant reduction in the primary outcome measures (total and new CEL) with daclizumab therapy over the 27.5 month course of the study. In addition, significant improvement in the secondary outcome measures (clinical rating scales and relapses) was also achieved. Monotherapy was effective in 57 patients for the duration of the study. However, 27 patients required reinstatement of interferon and an increase in daclizumab dose to better control disease activity. Therefore, monotherapy can be effective for some patients but others will require combination therapy for optimal disease suppression. The side effect profile was favorable throughout the study period. The mechanism of action for daclizumab in MS is under investigation. Blocking of binding of IL2 to the IL2R is one potential mechanism, however, augmentation of NK activity may play a role as well. A recent investigation of MS patients on therapy with daclizumab have implicated NK cell mediated regulation of T cells as an important mechanism of action (12). In summary, daclizumab is an effective therapy in patients that are not optimally controlled by interferon treatment alone. At the dosages evaluated in this study monotherapy can be effective but in some patients combination therapy may be beneficial. Persistent reductions in both total and new CEL were observed during the 27.5 months of treatment. Therapy also results in clinical benefits as measured by improvement in timed ambulation as well as EDSS and NRS. The effectiveness of the daclizumab therapy further supports a major role for immune mechanisms in the pathogenesis of multiple sclerosis. The results of the present study are supportive of further clinical trials with daclizumab in MS patients.

- 1) Daclizumab is well tolerated During 27.5 months of treatment.
- 2) Significant reduction in Total and New CEL are maintained during the Study Period.
- 3) Significant improvement in clinical parameters is observed.
- 4) Further evaluation in larger Phase II and Phase III trials will be required to establish the full efficacy and safety of Daclizumab in the treatment of MS.
- 5) Daclizumab therapy for MS remains investigational or off-label at this time.

Acknowledgements

The Cumming Foundation provided funding for the clinical trial. PDL Biopharma, Inc. supplied the Daclizumab. The investigators wish to thank the staff of the University of Utah Infusion Center and Rajiv Sharma research pharmacist for assisting with Daclizumab therapy. Dr. Roland Martin for providing the protocol adapted for this study.