Respiratory Medicine (2014) 108, 189–194

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/rmed

The potential additional benefit of infliximab in patients with chronic pulmonary sarcoidosis already receiving corticosteroids: A retrospective analysis from a randomized clinical trial

Marc A. Judson [a,*], Robert P. Baughman [b], Ulrich Costabel [c], Michael Mack [d], Elliot S. Barnathan [d]

[a] Division of Pulmonary and Critical Care Medicine, Albany Medical College, Albany, NY, USA
[b] University of Cincinnati Medical Center, Cincinnati, OH, USA
[c] Ruhrlandklinik, University of Duisburg-Essen, Essen, Germany
[d] Janssen Research & Development, LLC, Spring House, PA, USA

Received 12 November 2013; accepted 30 November 2013
Available online 10 December 2013

KEYWORDS
Sarcoidosis;
Pulmonary;
Corticosteroids;
Infliximab;
Treatment

Summary
Background: Infliximab, a TNF-alpha antagonist, has shown efficacy in the treatment of sarcoidosis. Since corticosteroids inhibit TNF-alpha expression, we postulated that sarcoidosis patients receiving a sufficient corticosteroid dose may have an attenuated response to the addition of infliximab.
Methods: We analyzed data from a previous randomized double blind prospective trial of infliximab versus placebo for chronic pulmonary sarcoidosis. The effect of the maintenance corticosteroid dose on the change in FVC % predicted between 0 and 24 weeks (ΔFVC%pred0-24) was analyzed in two ways. First, the mean ΔFVC%pred0-24 was calculated for the placebo and infliximab groups using three different daily prednisone equivalent dose thresholds: a) <10 mg versus ≥10 mg; b) <15 mg versus ≥15 mg; c) <20 mg versus ≥20 mg. Second, in both the placebo and infliximab groups, a correlation coefficient was calculated between the maintenance corticosteroid dose and ΔFVC%pred0-24.
Results: Both the group that received infliximab and either a maintenance daily dose of <10 mg of prednisone and the group receiving ≥10 mg had a significant increase in FVC% pred0-24. However, both the groups that received infliximab and a corticosteroid dose of

*Corresponding author. Division of Pulmonary and Critical Care Medicine MC-91, Albany Medical College, Albany, NY 12208, USA. Tel.: +1 518 262 0864; fax: +1 518 262 6472.
E-mail address: judsonm@mail.amc.edu (M.A. Judson).

http://dx.doi.org/10.1016/j.rmed.2013.11.019

>15 mg of prednisone and ≥20 mg of prednisone did not demonstrate a significant ΔFVC% pred0-24. For the placebo group, there was no significant correlation between the corticosteroid dose and the ΔFVC%pred0-24. For the infliximab group, there was a significant correlation ($p = 0.0097$) between higher corticosteroid dose and less improvement in FVC%pred0-24.
Conclusion: Our results suggest that infliximab adds minimal potential benefit to corticosteroids for pulmonary sarcoidosis at doses above 15—20 mg/day of prednisone.

Introduction

Infliximab has shown promise for the treatment of pulmonary and extrapulmonary sarcoidosis. In a prospective randomized clinical trial of chronic pulmonary sarcoidosis patients, infliximab improved the forced vital capacity (FVC) and lessened the degree of extrapulmonary sarcoidosis involvement by a statistically significant amount compared to those who received placebo [1,2].

Infliximab is a chimeric monoclonal antibody directed against tumor necrosis factor alpha (TNF-α). There is a sound rationale for using infliximab in the treatment of sarcoidosis because TNF-α is released by macrophages in patients with sarcoidosis [3], and TNF-α is thought to be integrally involved in the development of the sarcoid granuloma [4—6].

Although infliximab therapy has been used for the treatment of sarcoidosis for several years, there has been minimal attention paid to the effect of this drug in different subsets of sarcoidosis patients including those with specific organ involvement, specific demographic characteristics, and specific doses of additional other anti-sarcoidosis medications. We had anecdotally observed in our clinical practices that infliximab often failed to provide additional benefit to patients with pulmonary sarcoidosis who were receiving ≥20 mg of daily prednisone equivalent. Corticosteroids are recognized as the drug of choice for pulmonary sarcoidosis [7—9]. Corticosteroids have a broad spectrum of anti-inflammatory effects, including inhibiting TNF-α expression [10]. Since both infliximab and corticosteroids impair the activity of TNF-α, it is possible that pulmonary sarcoidosis patients who are receiving corticosteroids as a maintenance medication may have an attenuated response to infliximab. Because data concerning the effect of the maintenance corticosteroid dose on the infliximab response was available from a previously performed randomized double blind placebo controlled trial of infliximab for pulmonary sarcoidosis [1], we decided to retrieve these data and perform an analysis to determine the additional benefit of infliximab for pulmonary sarcoidosis based on the maintenance corticosteroid dose.

In this current report, we analyzed results of a previous randomized double blind prospective clinical trial of infliximab versus placebo for the treatment of chronic pulmonary sarcoidosis [1]. In that trial, a statistically significant improvement in the FVC at 24 weeks of therapy was found in those who received infliximab compared to those who received placebo (2.5% predicted, $P = 0.038$). This change in FVC was the primary endpoint of the trial. During the trial, subjects were required to be on a stable maintenance daily corticosteroid dose of ≥10 mg of daily prednisone equivalent and/or other immunosuppressive medications. In the current analysis, we sought to determine the impact of the maintenance corticosteroid dose on the change in % predicted FVC between 0 and 24 weeks in the infliximab and placebo groups. Our hypotheses were that a) the placebo group would not demonstrate a significant change in % predicted FVC regardless of the maintenance corticosteroid dose and b) the response of % predicted FVC to 24 weeks of infliximab treatment would be dependent on the concurrent maintenance prednisone dose, with higher doses leading to lower spirometric response.

Methods

The methods of the original trial have been described in detail elsewhere [1]. In brief, eligible patients were required to have histologically proven sarcoidosis, a diagnosis of sarcoidosis at least one year prior to screening, evidence of parenchymal lung sarcoidosis on chest radiograph, an FVC of ≥50% and ≤85% of predicted and a Medical Research Council dyspnea score of at least grade 1. Patients required treatment with at least 10 mg/d of prednisone or equivalent or one or more immunosuppressants for ≥3 months before screening. Doses of these medications had to be stable for ≥1 month before study entry. During the study, the background medication regimen and doses were to remain stable.

This was a phase 2, multicenter, double-blind, placebo-controlled study in which patients were randomized in a 1:1:1 ratio to receive intravenous infusions of placebo, infliximab 3 mg/kg, or infliximab 5 mg/kg at Weeks 0, 2, 6, 12, 18, and 24. A total of 138 patients from 34 centers in North America and Europe were randomized between September 30, 2003, and August 31, 2004. The primary endpoint was the change from baseline in the percent of predicted FVC at Week 24. The initial trial was approved by all Institutional review boards/ethics committees at the participating sites.

In the current analysis, subjects were included if they received a daily maintenance corticosteroid dose of greater than 0 during the trial. Similar to the initial trial, we combined the 3 mg/kg and 5 mg/kg infliximab groups as both had a significant positive response in the primary endpoint compared to placebo as the % predicted FVC response of the two infliximab doses were not statistically different from each other. The effect of the maintenance corticosteroid dose on the change in FVC % predicted between 0 and 24 weeks was analyzed in two ways. First, the mean change in % predicted FVC and the 95% confidence interval between 0 and 24 weeks was calculated for both the placebo and infliximab groups using three different