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LETTER TO THE EDITOR

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Conflict of interest statement

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Trial registration

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Infliximab therapy modulates an antigen-specific immune response in chronic beryllium disease

Chronic beryllium disease (CBD) is a granulomatous lung disorder that develops in 1–10% of beryllium-exposed workers.[1–4] While the natural history of CBD varies, increased respiratory symptoms, worsening chest radiography and pulmonary physiology are common.[5–9] Therapy for CBD is aimed at suppressing the beryllium-stimulated immune response, thus improving and/or stabilizing lung function. First line therapy is usually oral corticosteroids,[10–13] with other agents, such as methotrexate, used as steroid sparing therapy.[14–16] Despite numerous side effects, corticosteroids improve symptoms, chest radiographs and lung function in CBD. With treatment, while some patients may show a response initially, some patients with CBD worsen clinically.[10–13] There are limited alternate treatment options available.

We report herein, the first randomized, double-blinded placebo-controlled study undertaken to assess a TNF-α inhibitor, infliximab in treatment of CBD. Because of TNF-α's role in the initiation and perpetuation of granulomatous inflammation, we hypothesized that infliximab would result in improvement in Arterial-alveolar (A-aPaO_2) gradient after exercise (primary outcome), pulmonary function, quality of life and immune markers. The study was conducted at National Jewish Health (NJH) and the Hospital of University of Pennsylvania (HUP), based on a sarcoidosis trial.[17] We aimed to enroll 20 CBD subjects[2,8,18] on stable doses of corticosteroids and/or methotrexate, with no evidence of active or chronic infection, malignancy, other chronic disease, or past treatment with another biologic with a 3:1

infliximab:placebo ratio administered at 0, 2, 6, 12, 18 and 24 weeks. Of the 13 enrolled subjects, 8 in the infliximab treatment arm and 3 in the placebo arm completed the study, two withdrew before the first infusion before the sponsor stopped the study due to slow recruitment. Study endpoints included changes in testing from baseline to week 28 (four weeks post last infusion) in A-aPaO_2, lung function, SF-36, and blood and bronchoalveolar lavage (BAL) immune markers.

The demographics of participants were representative of a CBD population (8 males, 73% and 3 females, 27%) with a median (range) age of 56.5 (46–74) years. The three in the placebo arm were all former smokers, while only 3 of the 8 in the treatment arm were former smokers (5 were never). The median ± SD duration (years) of prednisone use was 5.5 ± 7.7 in the placebo group and 2.8 ± 1.6 in the treatment arm. There were no baseline differences in lung function (median ± SD FEV1 percent predicted: 84 ± 3.92 in placebo group, 72.5 ± 5.07 in treatment group; FVC percent predicted: 85 ± 7.79 vs. 69.5 ± 4.8; DLCO/VA: 61 ± 6.17 vs. 71.5 ± 6.27), chest radiography, quality of life, or immune markers between the placebo and treatment group. The A-a gradient at end of exercise was higher in the placebo group (75.47 ± 19.78 vs. 31.1 ± 6.16 in the treatment group, p = 0.014).

CBD allows the unique opportunity to assess changes in lung inflammation with treatment. Blood and BAL cells were obtained from placebo (n = 2 blood, n = 2 BAL) and infliximab treated CBD subjects (n = 8 blood, n = 5 BAL). Infliximab treatment tended to be associated with an increase in the absolute numbers of lymphocytes/cc in blood (median ± SD, 108 ± 14.6 × 10^4/cc vs. 170 ± 18.5 × 10^4/cc; p = 0.078) and the blood lymphocyte percent (p = 0.11). The median ± SD total BAL WBC count was reduced, 118.9 × 10^6 at baseline to 64.9 × 10^6 after infliximab treatment (p = 0.06) as was the WBC/cc (p = 0.06). In contrast to blood, a decline in the total number of BAL lymphocytes/cc was noted in the infliximab treated group (baseline median 9.9 × 10^4/cc [range: 2.7–40.2] to 7.3 × 10^4/cc [range: 0.8–20.9] after treatment; p = 0.06), along with a decline in percent lymphocytes (31% [range: 20.3–70.8] at baseline to 24% [range: 5.8–48.5]; p = 0.06). A decline in $CD4^+$ T cells was observed along with a decline in the $CD4^+$ beryllium-specific T cells expressing IFN-γ and TNF-α (p = 0.06). Conversely, an increase in the BAL percent macrophages was noted with infliximab treatment (58% baseline to 73%; p = 0.06). These changes suggest that infliximab therapy may decrease lung inflammation and the number of pathogenic, Be-responsive $CD4^+$ cells recruited to the target organ. Similar to our findings, in sarcoidosis subjects treated with infliximab there was a reversal of lymphopenia and increase in peripheral blood $CD4^+$ T cells.[19] The mechanism by which infliximab affects cell counts in the blood and BAL is unknown. In rheumatoid arthritis (RA), infliximab treatment appeared to reverse a dysfunctional blood T_{reg} cell population, with increase in the number and ability of the cells to suppress cytokine production.[20,21] We have recently shown that a deficient and dysfunctional population of natural T_{reg} cells are present in the lung of CBD subjects compared to those with beryllium sensitization without disease.[22]

With regard to clinical parameters explained in this study, our primary endpoint, the A-aPaO_2 proved to be technically problematic and no difference was found following infliximab treatment. No change was found in symptoms of dyspnea, FVC or chest

radiograph. As the sarcoidosis trial[17] noted improvement in a subgroup, we observed that those with a baseline diffusing capacity for carbon monoxide (DLCO) <80% predicted (n = 5, median ± SD, 65% ± 3.24), improved with treatment (72% ± 1.43, p = 0.06). A number of studies have found DLCO to be a good marker of CBD progression[6,7] and response to therapy.[10,11] Our power to detect clinically significant responses was limited because of small numbers of subjects with a range of disease severity.

We observed improvements in quality of life measures with treatment. The overall SF-36 mental score for the infliximab treated group demonstrated a sustained increase of 4.6 points (p = 0.08), while the placebo group dropped 7.5 points. Although no change was observed in the overall physical score, a sub-component, the Bodily Pain Score improved (54 at baseline to 84, p = 0.03). In clinical trials of Crohn's disease[23–26] and RA,[26–28] infliximab-treated groups showed improvement in quality of life scores. While subjects with RA, psoriasis and ankylosing spondylitis had lower physical and mental quality of life scores than our subjects,[27] the changes noted after treatment with infliximab were similar for CBD. In RA, similar to our study, the greatest change was noted in bodily pain scores, suggesting that infliximab reduces systemic inflammation even in a lung disease such as CBD. It is possible that CBD activity measures do not necessarily correlate with patient-reported health-related quality of life outcomes.[29,30] Since compliance is likely closely linked to patient's perception of health or improvement, improved SF-36 scores may inform physician–patient decisions regarding treatment options.

In summary, we describe the first clinical trial in CBD with infliximab. The study demonstrated alterations in the pulmonary immune response as a result of infliximab treatment. The mechanism by which infliximab affects this immune response is unknown, but may be more easily studied in CBD with evaluation of the specific components of a beryllium-stimulated immune response. Additionally, while our small numbers limited our ability to detect significant improvement in lung function, we observed an improvement in aspects of quality of life with treatment, and a suggestion that those with more severe gas exchange as indicated by DLCO may demonstrate clinical response.

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