Sarcoidosis: is there a role for anti-TNF-α?

Abstract
In severe cases of sarcoidosis treatment can be very difficult. The common treatment strategies might be failing. Tumour necrosis factor (TNF) α therapy is approved in rheumatoid arthritis, M. Crohn, psoriasis and ankylosing spondylitis. In sarcoidosis more recently a phase 2, multicenter, randomized, double-blind, placebo-controlled study was conducted in 138 patients with chronic sarcoidosis with pulmonary involvement. Patients in the combined infliximab groups (3 and 5 mg/kg) had a statistically significant improvement of the FVC (mean increase of 2.5% from baseline to week 24 in the percent of predicted FVC, compared with no change in placebo-treated patients (p=0.038)). Studies in the earlier mentioned diseases revealed that inadequate treatment responses could result from incomplete suppression of TNF α activity. This suggests that increasing patients’ dose or frequency of infliximab could in turn improve their clinical response. Further evaluation of anti-TNF therapy in symptomatic patients with severe, chronic sarcoidosis is needed.

Key-words: Sarcoidosis; tumour necrosis factor; TNF-α; infliximab

Introduction
Sarcoidosis is an antigen-driven, multisystem, granulomatous disorder, the cause of which is not known. In a genetically susceptible individual, antigen-presenting cells trap, process, and present the putative antigen, in the context of class II major histocompatibility complex (MHC) molecules, to CD4+ lymphocytes. The result of this union is a coordinated release of cytokines and chemokines, which recruit more inflammatory cells (lymphocytes, mononuclear phagocytes, and fibroblasts) and mount a granulomatous response dominated by interferon-γ and interleukin-12. Although the exact etiology remains unknown, current evidence supports
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The concept that the pathogenesis of sarcoidosis involves a highly polarized T-helper 1 (Th1) immune response to pathogenic tissue antigens or specific environmental factors. Granuloma formation is regulated by a complex interaction between T-helper lymphocytes and macrophages, in which cytokines such as tumour necrosis factor (TNF)-α play an important role (Fig. 1). In a small number of patients, profibrotic cytokines, including transforming growth factor-β and TNF-α, appear and move the inflammatory process towards fibrosis.

Treatment
The recommended treatments for sarcoidosis differ from none to a combination of cytotoxic agents. A major reason for this wide spectrum of treatment relates to the variation in disease presentation. The use of systemic therapy for sarcoidosis is usually driven by symptoms. There are several efficacious agents for the treatment of sarcoidosis (Table I). The common mechanism for action of these drugs is their effect on the immune response, especially the suppression of tumour necrosis factor (TNF), a key cytokine in chronic sarcoidosis. The absolute need for systemic therapy include manifestations which are life or organ threatening. In long term studies analyzing mortality from sarcoidosis, the most common causes of death are pulmonary, cardiac, neurologic, and hepatic. For respiratory impairment, a low vital capacity is a relative indicator of increased mortality. Moreover, treatment options vary because no treatment is a cure of the disease, but actually just a means to control symptoms. Conventional treatment is focused on attenuating granuloma formation with antimalarial drugs that inhibit antigen presentation or with non specific anti-inflammatory agents such as glucocorticosteroids, methotrexate, or azathioprine. Anti-TNF-α agents such as Infliximab and thalidomide have recently shown some success in sarcoidosis (see also chapter R.P. Baughman). The design of future therapies depends, among others on the improved knowledge of the critical immunological processes operative in different stages of disease.

Infliximab
The anti-TNF-α agent infliximab (Remicade®) is a recombinant immunoglobulin G1-κ (IgG1-κ) human-murine chimeric monoclonal antibody that specifically and potently binds and neutralizes the soluble TNF-α homotrimer and its membrane bound precursor. The high-affinity binding prevents the interaction of TNF-α with its cellular receptors, attenuating inflammatory and other deleterious effects related to TNF overproduction. Many case reports are published illustrating the efficacy of Infliximab. Favorable results are also found in patients treated in our hospital (see also Figures 3 and 4). To assess the efficacy of infliximab in sarcoidosis a phase 2, multicenter, randomized, double-blind, placebo-controlled study was conducted in 138 patients with chronic sarcoidosis. Patients were randomized to receive intravenous infusions of infliximab (3 or 5 mg/kg) or placebo at weeks 0, 2, 6, 12, 18, and 24 and were then followed through week 52. The primary endpoint was the change from baseline to week 24 in percent of predicted forced vital capacity (FVC). Patients in the...
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Fig. 1 – Hypothetical model of the pathogenesis of sarcoidosis. An inciting agent induces antigen-specific, Th1-mediated granulomatous inflammation with production of Th1 cytokines such as interferon (IFN)-γ and interleukin (IL)-2. Macrophages, activated directly by the inciting agent and by IFN-γ, produce IL-12, TNF-α, IL-6 and other cytokines important in cell activation, proliferation and recruitment. Activated macrophages and T-cells along with other effector cells such as fibroblasts, orchestrate the complex process of granuloma formation under the regulatory influence of local cytokine production. Removal of inciting agent allows immunosuppressive cytokines such as tumour growth factor (TGF)-β to down regulate the immune response with return to cytokine homeostasis. Granuloma regression likely occurs by cell apoptosis. Persistent antigenic stimulation results in cytokine dysregulation and possibly T-cell autoimmune responses. If untreated, chronic antigenic stimulation and cytokine production results in tissue injury which, together with up regulated production of TGF-β and other profibrotic cytokines, lead to irreversible fibrosis (adapted from Moller).
combined infliximab groups (3 and 5 mg/kg) had a statistically significant improvement of the FVC (mean increase of 2.5% from baseline to week 24 in the percent of predicted FVC, compared with no change in placebo-treated patients (p=0.038, see Fig. 2)). Results of post hoc exploratory analyses suggested that patients with more severe disease tended to benefit more from infliximab treatment. No significant differences between the treatment groups were observed for any of the major secondary endpoints at week 24. Further evaluation of anti-TNF therapy in symptomatic patients with severe, chronic sarcoidosis is needed.

Experience from other studies
Recent clinical experience in rheumatoid arthritis (RA) patients who are being treated with intermittent (every 8 weeks) pulse Infliximab therapy indicates that in some patients the disease flares a few days or weeks before their next pulse therapy. This was recently found to correlate with the serum levels of infliximab. Inadequate suppression of serum TNF-α level after infliximab infusion in RA patients with active disease was demonstrated. RA patients with active disease had significantly higher levels of serum TNF-α which could not be suppressed by infliximab. Therefore, it was hypothesized that inadequate treatment re-

Table I – Drug therapy for sarcoidosis

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug Description</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>Prednisone</td>
<td>5-40 mg</td>
<td>Initial dose higher, reduce to minimal tolerable and effective dose</td>
</tr>
<tr>
<td></td>
<td>Prednisolone</td>
<td>5-40 mg</td>
<td></td>
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<tr>
<td></td>
<td>Budesonide</td>
<td>800-1600 ugm</td>
<td>Inhaled therapy</td>
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<tr>
<td></td>
<td>Triamcinolone</td>
<td></td>
<td>Used in topical therapy for skin</td>
</tr>
<tr>
<td>Cytotoxic</td>
<td>Methotrexate (MTX) with folic acid</td>
<td>5-15 mg once a week</td>
<td>Takes up to 6 month to be effective</td>
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<tr>
<td></td>
<td></td>
<td>5 mg once a week</td>
<td></td>
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<tr>
<td></td>
<td>Azathioprine</td>
<td>50-250 mg daily</td>
<td>More leukopenic than MTX</td>
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<tr>
<td></td>
<td>Chlorambucil</td>
<td>2-12 mg daily</td>
<td>Higher rate of malignancy than other agents</td>
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<tr>
<td></td>
<td>Leflunomide</td>
<td>10-20 mg daily</td>
<td>Similar to MTX, but less nausea</td>
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<tr>
<td></td>
<td>Cyclophosphamide</td>
<td>50-150 mg oral daily</td>
<td>Higher rate of side effects, but associated with higher response rate than other cytotoxic agents</td>
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<tr>
<td></td>
<td></td>
<td>500-2000 mg intravenously every 2 weeks</td>
<td></td>
</tr>
<tr>
<td>Anti-microbial agents</td>
<td>Chloroquine</td>
<td>200-400 mg daily</td>
<td>Less ocular toxicity than chloroquine</td>
</tr>
<tr>
<td></td>
<td>Hydroxychloroquine</td>
<td>200-400 mg daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Minocycline</td>
<td>100-200 mg daily</td>
<td>Rarely associated with immune toxicity</td>
</tr>
<tr>
<td>Cytokine modulation</td>
<td>Pentoxifylline</td>
<td>200-400 up to three times a day</td>
<td>High doses may be needed to block TNF.</td>
</tr>
<tr>
<td></td>
<td>Thalidomide</td>
<td>50-200 mg daily</td>
<td>Teratogenic potential major concern</td>
</tr>
<tr>
<td></td>
<td>Infliximab</td>
<td>5 mg/kg intravenously every 4-8 weeks after loading doses</td>
<td>Increase rate of infection and allergic reaction</td>
</tr>
</tbody>
</table>
responses could result from incomplete suppression of TNFα activity. This suggests that increasing patients' dose or frequency of infliximab could in turn improve their clinical response. For patients with inadequate response, dose per infusion can be increased to as much as 10 mg/kg, or the frequency of infusions can be increased to once every 4 weeks.

Fig. 2 – Primary endpoint, change from baseline in percentage predicted FVC at week 24.

Fig. 3 – HRCT features of a patient with severe sarcoidosis not responding to the conventional therapy. Left: before treatment with Infliximab, right: after 6 months treatment with Infliximab. There is a substantial improvement of the micronodular lesions and the consolidation.

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There is growing evidence that substantial numbers of patients who receive infliximab have their dose and/or frequency of infusions increased. Many patients with RA who receive infliximab experience dose intensification within the first year of therapy. Moreover, analysis of data from ATTRACT, a placebo-controlled double-blind, randomized clinical trial of infliximab in patients with active RA refractory to MTX treatment, showed that clinical improvement of RA is dose-related and that higher trough levels of infliximab may be beneficial for patients with RA. Whether this theory holds true in clinical practice and whether to increase the infusion dose or the frequency of their infusions are questions that remain unanswered. This applies similarly to other autoimmune and inflammatory disorders in which TNF-α plays an important role, such as ankylosing spondylitis (AS), psoriasis and sarcoidosis. The concomitant use of immunosuppressive agents like methotrexate or azathioprine in order to reduce immunogenicity and increase the long-term efficacy of infliximab has to be further investigated.

Conclusion
It is tempting to speculate that in sarcoidosis a reduction of the time between infusions may reveal greater therapeutic benefit, but this remains to be proven. Moreover, it remains to be seen if serum TNF-α levels could be used as guide in determining the dose and intervals between dosing of anti-TNF therapy in order to achieve the desired clinical response. If true, this may indicate what many providers believe that the recommended initial dose of infliximab is too low, a belief supported by the need for dose escalation in many patients. This underlines the need for future studies to explore the real benefit for severe sarcoidosis patients of appropriate anti-TNF therapy.

References