Tumor necrosis factor inhibition in the treatment of refractory sarcoidosis: slaying the dragon?

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Tumor Necrosis Factor Inhibition in the Treatment of Refractory Sarcoidosis: Slaying the Dragon?

Saint George, the symbol for the World Association for Sarcoidosis and Other Granulomatous Diseases (WASOG), has long been known as the “dragon slayer”; his pictures show a brave knight in battle with a fierce dragon; sometimes, a beautiful princess is present. Saint George is fighting an evil monster with multiple heads to protect God’s truth.

Sarcoidosis is a chronic granulomatous disease of unknown etiology that affects every organ system and has various presentations, like a dragon with multiple heads. The treatments for sarcoidosis represent different types of swords. Glucocorticoids are a broadsword, inhibiting many of the inflammatory pathways activated in the disease. Methotrexate, thalidomide, and chloroquine have a more limited antiinflammatory effect, mostly directed towards the activated macrophage. And while the US Food and Drug Administration has not approved a therapy for sarcoidosis, several have become standard therapy for a subset of sarcoidosis patients.

Granulomas are created by macrophages, epithelioid cells, giant cells, and T cells. Increased tumor necrosis factor-α (TNF-α) secretion by alveolar macrophages is found in patients who have progressive pulmonary disease. Another feature of sarcoidosis is anergy. A recent study by Miyara, et al demonstrated that CD4+CD25brightFoxP3+ cells accumulated at the periphery of sarcoid granulomas. These T regulatory cells have potent antiproliferative activity, including the suppression of TNF, and may account for anergy. It has been suggested that the compartmentalization of the inflammatory response can explain why some areas such as the lung have intense inflammation, while a T cell influx, while other areas, such as the peripheral blood, can have lymphopenia.

The immune response is variable in different organs of the same sarcoidosis patient. The clinical response to sarcoidosis is also variable. Some patients have an acute, self-limited form of the disease: within 2 to 5 years, their disease resolves, with no need for further therapy. In the United States, this represents about 75% of sarcoidosis patients. In a subgroup of patients the sarcoidosis is chronic, requiring years of treatment. Treatments targeting TNF are used in these chronic patients.

Specific inhibition of TNF using the biological agents etanercept, infliximab, or adalimumab has been effective in the treatment of rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, and various inflammatory conditions. Infliximab but not etanercept is effective in treating Crohn’s disease, a granulomatous process. Etanercept was also not found to be effective as an additional agent in treating patients with Wegener’s granulomatosis.

Infliximab has been extremely effective for some cases of refractory sarcoidosis. A multicenter, randomized, double-blind, placebo-controlled study of 138 patients with chronic pulmonary sarcoidosis treated with infliximab showed a statistically significant improvement in forced vital capacity after 24 weeks of therapy, the primary endpoint of the study. Adalimumab has been used with success in some patients with therapy-resistant sarcoidosis. Etanercept was found to be effective in occasional case reports of patients with sarcoidosis. However, in a randomized trial of ocular sarcoidosis, etanercept was no better than placebo.

Disease heterogeneity and differences in pharmacokinetics, pharmacodynamics, and mechanisms of action may account for these effects. Reverse-signaling by transmembrane TNF in response to infliximab and adalimumab, but not etanercept, might also influence the therapeutic response. Also, infliximab, but not etanercept, leads to cell lysis of active inflammatory cells releasing TNF in patients with Crohn’s disease.

In this month’s issue of The Journal, Sturfelt, et al report a case of neurosarcoidosis occurring in a patient with rheumatoid arthritis treated with infliximab and metho-

See Neurosarcoidosis in a patient with RA during treatment with infliximab, page 2313
trexate\textsuperscript{11}. This follows several other reports of cases of sarcoidosis-like disease during treatment with etanercept\textsuperscript{12-14} or infliximab\textsuperscript{15}. The time course of development varied from 6 months to 5 years. Development of sarcoidosis months after initiation of therapy argues against a simple drug allergy as the cause of the granulomas. Most cases occurred in patients receiving etanercept for rheumatoid arthritis, while one occurred secondary to infliximab for ankylosing spondylitis. The mostly European cases presented with mediastinal adenopathy, skin manifestations, and/or mild pulmonary symptoms. Signs and symptoms resolved after discontinuation of therapy.

Since the etiology of sarcoidosis is unknown, diagnosis is always in question. However, there is consensus on a diagnosis of sarcoidosis if granulomas are present in 2 or more organs and granulomas have been confirmed by histology in at least one area. However, other causes for granulomas should first be ruled out\textsuperscript{1}. In the cases reported here of anti-TNF therapy-associated sarcoidosis, the authors were careful to exclude other causes of granulomatous diseases, especially tuberculosis. The use of an anti-TNF agent may allow infection or reactivation of a less virulent mycobacterial or fungal organism, leading to a granulomatous response. Such an organism may be difficult to detect with standard methodology. We are not aware of any detailed, broad-based polymerase chain reaction (PCR) evaluation of granulomas from patients with anti-TNF-associated sarcoidosis. There are reports using PCR to detect nontuberculous mycobacteria in some patients with sarcoidosis-like condition\textsuperscript{16}. These questions remain the subject of ongoing investigations.

TNF inhibition has been associated with induction or worsening of various autoimmune diseases, systemic lupus, vasculitis, interstitial lung disease, psoriasis, and Crohn’s disease\textsuperscript{17}. New onset or severe exacerbation of psoriasis has been described as a rare complication of TNF-\(\alpha\) inhibitor therapy. Increased production of interferon-\(\alpha\) in TNF-\(\alpha\)-inhibitor-associated psoriasis has been proposed as a pathophysiologic explanation for this reaction\textsuperscript{18}. Treatment of hepatitis C with recombinant interferon-\(\alpha\) has been associated with development of sarcoidosis\textsuperscript{19}.

TNF is a factor in the initiation and maintenance of granulomas. TNF knockout mice exposed to Mycobacterium do form granulomas, but the granulomas are smaller and more likely to become apoptotic\textsuperscript{20}. This is similar to the resolution of granulomas in the acute, self-limited form of sarcoidosis\textsuperscript{1,5}. In addition, T regulatory cells, which suppress TNF release, are found on the periphery of granulomas in sarcoidosis patients with acute disease\textsuperscript{4}; however, the exact role of Treg cells in the pathogenesis of sarcoid granulomas remains unknown.

In addition, anti-TNF therapy does not lead to continuous total suppression of TNF. Changes in the level of TNF may allow granulomas to form. Rebound, higher levels of TNF may be encountered even with anti-TNF therapy\textsuperscript{21}. It is interesting to note that most case reports to date of sarcoidosis associated with anti-TNF therapy occurred in patients being treated with etanercept.

The balance of the inflammatory response in sarcoidosis seems to be a key aspect of the variable nature of the clinical course of the disease\textsuperscript{1,2}. While an initial manifestation of sarcoidosis is the formation of granulomas, it is the response to these granulomas that determines the clinical course of the patient. In most patients granulomas resolve over the following 2 to 5 years, with or without therapy\textsuperscript{5}. In those with chronic disease, cytokines such as TNF and interleukin 8 seem to persist\textsuperscript{2,3}.

To date, sarcoidosis occurring during anti-TNF therapy appears to be self-limiting. Anti-TNF therapy has been used for chronic sarcoidosis. Patients with chronic disease have granulomas that are already well established and continue to worsen despite therapy\textsuperscript{7,8}. Agents such as cyclosporine, which inhibit CD-4 function, have a limited role in these patients\textsuperscript{1}. Not all patients with refractory sarcoidosis respond to anti-TNF therapy\textsuperscript{8}. Therefore, it is not surprising that a single, targeted therapy may be associated with appearance of sarcoidosis. This might be the result of a “break through” of the disease, altered cytokine balance, increased interferon-\(\alpha\) levels, rebound TNF secretion, or exposure to an infectious agent that stimulates the granulomatous process, or to a combination of these factors.

While Saint George is usually shown brandishing a single sword to fight the dragon, the American Thoracic Society recommends several swords in order to target sarcoidosis-associated hypercalcemia, and cardiac, ocular, and neurologic sarcoidosis\textsuperscript{1}. It is not clear which is the best sword to use and what is the best time to declare war on this dragon with multiple heads. Anti-TNF therapy may be able to slay a major part of the disease. However, as any gardener will tell you, pruning one part of the plant may allow another bud to grow. Therefore, constant monitoring of the patient remains crucial in the management of sarcoidosis.

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