Infection and Anti-Tumor Necrosis Factor-Alpha Therapy

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Biological drugs are a revolution in the treatment of rheumatoid arthritis and Crohn's disease. Today they are being utilized in a variety of other rheumatologic diseases such as spondyloarthropathies (psoriatic arthritis, ankylosing spondylitis, reactive arthritis), vasculitis, myositis, uveitis, and others. Anti-tumor necrosis factor-alpha agents are proof that the manipulation of one molecule can effectively deter the inflammatory process even in long-standing disease. Furthermore, when compared with other immunosuppressive therapies routinely utilized in rheumatoid arthritis, the biological agents have a very good safety profile.

Infections are inherently common in patients with rheumatic disorders. Predisposing factors for such vulnerability include alterations of immunoregulation, disease severity, debility, comorbid illnesses, and the use of immunosuppressive medications. The more common infections are septic arthritis, cellulitis and respiratory tract infections. Opportunistic infections have been observed with low dose methotrexate, cyclophosphamide and azathioprine, with or without corticosteroids [1].

The advent of new biological agents has precipitated further investigation of the links connecting infection, the underlying disease and its treatment, resulting in several interesting observations. Interleukin-1 and TNFα, the major pro-inflammatory cytokines, play important roles in host defense against infection. Inhibition of their activity could therefore be expected to augment the risk of infection in patients with preexisting abnormalities of immune regulation [1,2]. Rodent studies using live infection models have shown that neutralization or gene deletion for TNFα is frequently associated with a reduction of host defense in models of live Gram-positive or Gram-negative infections and increased infection by intracellular microbes such as *Salmonella* and *Listeria*. The absence of the interleukin-1 receptor can also result in decreased resistance to *Listeria* or Gram-positive bacteria, and TNFα and interferon-gamma are required for defense against infection caused by *Mycobacterium tuberculosis* [3].

Methods of reporting adverse effects of a drug, e.g., opportunistic infections, include post-marketing, post-licensure surveillance, and publications in Medline. The true number of opportunistic infections is probably underreported. Anti-TNFα agents (infliximab and etanercept) have been administered widely in the last 4 years. In the ATTRACT study (Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy), 44% of patients in the infliximab cohort were treated with antibiotics compared to 35% of patients who received methotrexate alone, but the frequency of serious infections requiring hospitalization was similar in both groups (8% vs. 6%) [4].

Post-marketing resources indicate that infections are a potential adverse effect that should be monitored. The periodic safety updates (termed PSUR) are provided every 6 months by the pharmaceutical company. Comprehensive coverage of infliximab adverse events since August 1998 was based on all clinical trials, follow-up, and post-marketing reports including registries. No increase in incidence of any adverse events, no new adverse events previously undetected, and a high benefit-to-risk ratio of infliximab therapy were the key observations based on PSUR-6 (i.e., after 3 years) [5].

The potential serious adverse effects that are being monitored are tuberculosis and opportunistic infections, antibodies to infliximab and infusion reactions, the development of autoantibodies and autoimmune diseases, cardiovascular events, neurologic events, neoplasms/lymphomas, and death.

Listeria

In this issue of *IMAJ*, Tweezer-Zaks et al. [6] report on two Israeli patients (one with rheumatoid arthritis and the other with Crohn's disease) who developed *Listeria* infection while on infliximab therapy. Interestingly, the patient with Crohn's disease developed the opportunistic infection after a single dose. Both patients were treated accordingly and recovered. *Listeria* is the second most reported opportunistic infection, following TB, associated with anti-TNFα therapy. Listeriosis is more common in rheumatoid arthritis than in Crohn's disease, and more common in patients treated with infliximab. Reports from the U.S. Food and Drug Administration Adverse Event Reporting System, a pharmaco-vigilance program, suggest that the number of patients with *Listeria* may be higher than those reported by post-marketing. In a U.S. study [7], 26 cases of *Listera* infection led to 8 deaths in patients receiving infliximab or etanercept. The majority of patients (92%) were treated with infliximab, 64% had rheumatoid arthritis, while 36% had Crohn's. Interestingly, in this group, infection developed soon after initiation of therapy (median of 2.5 doses), the patients had serious infection

TNFα = tumor necrosis factor-alpha

TB = tuberculosis

reported as sepsis or meningitis, and some were treated (in addition to methotrexate) with more than one concomitant immunosuppressive agent (prednisone, azathioprine, cyclosporine). The median age of the patients was high (69.5 years) and co-morbidity, such as diabetes, was not assessed [7].

Tuberculosis

The cumulative exposure and reporting rates for TB indicate that it is the most common opportunistic infection related to anti-TNFα therapy: 277 cases among 462,187 cumulative exposures to infliximab (0.06%). The characteristics of TB patients treated with infliximab revealed that most cases were outside the United States (69%), there were more women (62.5%) than men, the median age was 56.2 years (range 17–86), the disease was more common in patients with rheumatoid arthritis (62.1%) than with Crohn's disease (20.2%), and there were 28 deaths. Pulmonary TB was the most common form of disease (69.1%) and miliary TB was less common (20.6%) [8]. Other authors, however, purport that miliary TB is more common [9].

Interestingly, the majority of post-infliximab TB cases occur after the first few infusions. Consistent with the hypothesis is that immunosuppression with any anti-TNFα drug can cause reactivation of TB in individuals who are unknowingly exposed. However, the number of patients exposed to infliximab continues to increase, whereas the number of cases of TB declined during PSUR-6, probably reflecting earlier diagnosis and extensive physician educational efforts, including mandatory purified protein derivative testing and chest radiograph prior to the institution of therapy. Guidelines recommend that patients with evidence of prior TB should be treated before receiving anti-TNFα treatment. Those patients with a positive PPD test but a normal chest X-ray should receive isoniazid as prophylaxis [8,9]. Finally, the overall TB fatality rate in PSUR-6 declined from previous periods.

Other opportunistic infections associated with infliximab and etanercept in post-marketing reports are also a potential serious problem if not detected. The reported opportunistic infections leading to death are shown in Table 1 [5].

Table 1. Reported post-marketing infections In patients treated with infliximab other than TB [5]

	PSUR-5		PSUR-6	
Infection	**Cases**	**Deaths**	**Cases**	**Deaths**
All oportunistic infections	80	20	104	14
Pneumocystic carinii pneumonia	12	3	10	2
Salmonellosis	12	1	1	0
Atypical *Mycobacteria*	10	3	20	0
Histoplasmosis	9	3	8	1
Listeriosis	9	3	9	3
Aspergillosis	5	2	13	3
Coccidioidmycosis	5	1	9	4
Cytomegalovirus	5	2	6	1
Cryptococcosis	4	1	8	0
Systemic candidiasis	2	1	4	0
Mucormycosis	1	0	1	0

Histoplasmosis

Ten cases of *Histoplasma capsulatum* infection were reported: 9 associated with infliximab and 1 with etanercept. In patients treated with infliximab, manifestations of histoplasmosis occurred within 1 week to 6 months after the first dose and typically included fever, malaise, cough, dyspnea and interstitial pneumonitis. Of the 10 patients with histoplasmosis, 9 required treatment in an intensive care unit, and 1 died. All patients had received concomitant immunosuppressive medications in addition to infliximab or etanercept, and all resided in *Histoplasma capsulatum*-endemic regions. Post-licensure surveillance suggests that acute life-threatening histoplasmosis may complicate immunotherapy with TNFα antagonists, particularly infliximab. Histoplasmosis should be considered early in the evaluation of patients who reside in such endemic areas and in whom infectious complications develop during treatment with infliximab or etanercept [10].

There is one case report of a patient who developed pneumocystic pneumonia [11] and one report on invasive aspergillosis [12], but no reports in Medline on infections such as salmonellosis, atypical *Mycobacteria*, coccidioidmycosis, cryptococcosis, mucormycosis, or *Candida*. Viral infection with cytomegalovirus was reported in a 65 year old patient with Crohn's disease following a single dose of infliximab. Deterioration in the primary disease should raise the suspicion of opportunistic infection [13].

Other microorganisms leading to infection were recently reported in 11 patients with rheumatoid arthritis while on anti-TNFα therapy [14]. Infection with *Streptococcus pneumoniae*, *Legionella pneumonia*, *Staphylococcus aureus*, *Staph. lugdunensis* and *Proteus mirabilis* was described. Six patients were receiving infliximab and five patients etanercept. No deaths were reported. The shortest interval between initiation of therapy and infection was 22 weeks; there was no clustering of infections at any point interval, as seen with reactivation of TB. The findings showed a clear difference in the incidence of serious infections before compared with after anti-TNFα therapy. In this group, 18.3% had a serious infection [14].

Why some patients, but not others, succumb to rapidly disseminated infection is unknown but may be related to the extent of TNF inhibition in different individuals. Most rheumatoid arthritis patients have already been treated with long-term, multiple disease-modifying anti-rheumatic drugs, indicating that partial immunosuppression exists prior to anti-TNFα therapy. Caution is advised in patients with recurring infections and in those with severe co-morbidities – for example, poorly controlled diabetes mellitus or heart failure – particularly older patients. Infection may mimic exacerbation of the primary disease. Administration of live vaccines to patients taking these drugs is not recommended, but patients should be brought up to date with all immunizations relevant to their age group before commencement of therapy [2]. Furthermore, physicians should be aware that

PPD = purified protein derivative

opportunistic infections may occur early in anti-TNFα therapy, even after a single dose; and the reporting of any suspected drug-related adverse event should be encouraged. Long-term observation will be required to determine the exact nature of the relationship between cytokine inhibition and infection.

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