

Mycobacterial and Other Serious Infections in Patients Receiving Anti-Tumor Necrosis Factor and Other Newly Approved Biologic Therapies: Case Finding through the Emerging Infections Network

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(See the editorial commentary by Iseman and Fischer on pages 1741–2)

We present the results of a nationwide survey of infectious disease consultants to identify mycobacterial and other serious infections in patients receiving anti-tumor necrosis factor compounds and other novel targeted therapies. Nontuberculous mycobacterial infections, histoplasmosis, and invasive *Staphylococcus aureus* infection were all reported more frequently than was tuberculosis disease in this context.

The epidemiology of *Mycobacterium tuberculosis* infection is well described, but less is known about nontuberculous mycobacterial (NTM) infections. There is widespread belief that NTM infections are increasingly common, particularly among women [1]. These infections may be of increasing importance as newer biologic, immunosuppressive agents are used to treat autoimmune inflammatory conditions [2]; many of these conditions cause structural lung disease (e.g., rheumatoid arthritis) and predispose to NTM disease [1]. To date, both tuberculosis (TB) and NTM infections have been reported in association with use of biologic therapies that inhibit TNF- α , including infliximab (Remicade), adalimumab (Humira), and etanercept (Enbrel). The most recent review of the Food and Drug Administration's MedWatch database found that reports of anti-

TNF- α -associated TB were 5–10 times more common than reports of NTM and other granulomatous infections [3]. To date, much attention has focused on TB prevention in patients using anti-TNF- α agents, but little is known about the types and relative frequencies of NTM infections in this context.

Accordingly, we surveyed infectious disease specialists to better understand the spectrum and consequences of TB and NTM infections in patients receiving anti-TNF- α therapy. In addition, because of the recent Food and Drug Administration approval of other biologic immunosuppressant agents to treat rheumatoid arthritis, we were also interested in infections potentially related to those agents. Abatacept (Orencia) binds CD80/CD86 receptors on antigen-presenting cells and subsequently mitigates T lymphocyte activation and cytokine release. Rituximab (Rituxan), first approved for the treatment of lymphoma, is an anti-CD20 monoclonal antibody that selectively depletes peripheral B lymphocytes. To date, there are no published reports of mycobacterial infection associated with use of these new agents.

Methods. In June 2007, we surveyed Infectious Diseases Society of America members of the Emerging Infections Network (EIN). Approximately 15% of the Infectious Diseases Society of America's members participate in the EIN. We asked each member to report all cases of TB and NTM infections that their patients experienced during the previous 6 months. Members who did not respond were resurveyed 2 and 4 weeks later. For cases that occurred in patients receiving anti-TNF- α agents, abatacept, or rituximab, we asked members to provide further clinical details, including the biologic agent used at the time of diagnosis of infection, concomitant use of prednisone or methotrexate, death during treatment for mycobacterial infection, whether biologic therapy was stopped after mycobacterial infection diagnosis, and whether immune reconstitution inflammatory syndrome (IRIS) occurred. We also asked members to report cases of other infections that they had seen in the previous 6 months in patients who received these specific biologic agents.

Results. Four hundred twenty-six (48.9%) of 871 EIN members responded. The responding members reported a total of 1876 mycobacterial infections occurring in the previous 6 months; 1021 (54%) were NTM infections, and 855 (45%) were TB. Respondents were located throughout the United States and Canada, as follows: eastern states (43% of respondents), central states (35%), mountain states (4.5%), Pacific states (15.0%), US territories (0.5%), and Canada (2.0%). Of all reported mycobacterial infections, 49 (2.6%) occurred in patients

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who received biologic therapies. In this context, NTM infections were reported nearly twice as frequently as TB (32 cases vs. 17 cases). *Mycobacterium avium* complex was the most frequently reported NTM species, causing infection in 16 patients (figure 1). The remaining pathogens that caused biologic therapy-associated NTM infections included *Mycobacterium chelonae* ($n = 5$), *Mycobacterium abscessus* ($n = 3$), *Mycobacterium marinum* ($n = 3$), and others ($n = 5$; *Mycobacterium fortuitum*, *Mycobacterium haemophilum*, *Mycobacterium kansasii*, and *Mycobacterium scrofulaceum*). The median age of patients with biologic therapy-associated mycobacterial infections was 57 years (range, 11–82 years). At the time of diagnosis, 18 patients were receiving infliximab, 12 were receiving etanercept, 8 were receiving rituximab, 3 were receiving adalimumab, and 8 were receiving unspecified biologic therapy. Twenty-one (43%) of 49 patients with biologic therapy-associated mycobacterial infections were receiving concomitant prednisone and/or methotrexate therapy. In most patients (42; 86%), biologic therapy was stopped when infection was diagnosed. Overall, only 2 patients (4%) experienced IRIS; one case occurred in an etanercept-treated patient with TB, and the other case occurred in an infliximab-treated patient with *M. marinum* infection. Eight (16%) of 49 patients with biologic therapy-associated mycobacterial infections died during their treatment for mycobacterial infection. Of these deaths, 3 occurred in patients with TB, 2 occurred in patients with *M. chelonae* infection, and the remaining deaths occurred in patients with *M. marinum*, *M. kansasii*, or an unspecified NTM infection.

A variety of other nonmycobacterial infections were also reported in association with biologic therapies. The most commonly described serious infections were invasive *S. aureus* infection (in 73 cases) and histoplasmosis (56), followed by severe pneumococcal disease (20), cytomegalovirus (18), aspergillosis (16), and parasitic infections (10). Other reported infections included listeriosis, legionellosis, blastomycosis, coccidioidomycosis, and salmonellosis (2–5 cases each).

Discussion. Our survey resulted in a high response rate and a large number of reported anti-TNF- α therapy-associated infections. Of note, NTM infections were reported twice as often as TB, and infections due to *M. avium* occurred nearly as frequently as TB. Very few patients experienced IRIS when their biologic therapy was stopped during infection treatment, and a high percentage of patients died while receiving antimycobacterial therapy.

To date, available published data regarding intracellular pathogens occurring in anti-TNF- α -treated patients in the United States have been derived from the passive MedWatch surveillance system, which is subject to underreporting. The last review of this database suggested that TB was more common than NTM infections in patients receiving anti-TNF- α therapy [3]. Our survey suggests that the reverse might be true in the United

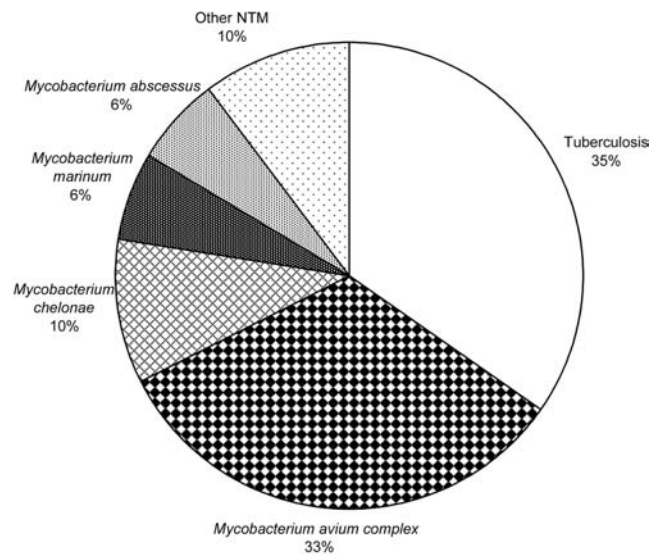


Figure 1. Reported types of mycobacterial infection ($n = 49$) associated with biologic agents. Infliximab was associated with 11 cases of tuberculosis and 7 nontuberculous *Mycobacteria* (NTM) infections, etanercept was associated with 4 cases of tuberculosis and 8 NTM infections, rituximab was associated with 3 cases of TB and 5 NTM infections, adalimumab was associated with 1 case of TB and 2 NTM infections, abatacept was not associated with any infection, and unspecified biologic therapy was associated with 2 cases of tuberculosis and 6 NTM infections.

States. This finding is not surprising, given the low prevalence of TB in the United States, the use of isoniazid to treat infection in high risk patients, and the possibility that the incidence of NTM disease is increasing [1]. Unlike TB, NTM disease is not a public health reportable disease, more difficult to diagnose, generally more insidious in onset and progression, and probably less likely to be reported as an infectious complication to the MedWatch system.

The Centers for Disease Control and Prevention and others have published recommendations for screening and treatment for latent TB prior to the initiation of anti-TNF- α therapy [4]. Although it is clear that screening can decrease the risk of TB among such patients [5], it is less clear what should be done for patients who develop TB while they are already receiving anti-TNF- α therapy. There have been reports of IRIS in patients with TB who stopped their anti-TNF- α therapy at the time of TB treatment initiation [6]. These reports, coupled with very limited data suggesting that concomitant etanercept therapy during TB treatment might be safe [7], raise the question of whether anti-TNF- α therapy should be stopped if TB is diagnosed. However, our survey findings suggest that IRIS reactions are not common. Because of the high mortality rate reported in our series, it seems prudent to stop anti-TNF- α therapy if patients develop mycobacterial disease during the treatment.

Interestingly, a handful of mycobacterial infections were reported in patients receiving rituximab. Rituximab typically depletes peripheral CD20⁺ B lymphocytes for 6–12 months with each treatment course. To our knowledge, these are the first reports of mycobacterial infections in patients using this compound. This compound is approved for use to treat both rheumatoid arthritis and non-Hodgkin lymphoma. Currently, there is no recommendation to screen patients for TB prior to the use of rituximab therapy. There is emerging evidence that B lymphocytes might play an important role in the containment of such infections. Maglione et al. [8] recently found that, in a murine TB model, B cells were an important constituent of granulomas and that B cell knockout mice failed to contain TB infections and were more likely to die than were mice with intact B cell populations. B lymphocytes are also present in the outer portion of granulomas in human lung tissue infected with TB [9].

Lastly, our survey highlights the importance of extracellular pathogens in the context of biologic therapy. Our network reported more invasive *S. aureus* infections than any other infection type in our survey. Anti-TNF- α agents are frequently used in patients known to have high rates of colonization with and infection due to *S. aureus*, such as those with rheumatoid arthritis or psoriasis. Although no previous studies have addressed whether anti-TNF- α therapy increases the risk of invasive *S. aureus* infection, observational studies suggest that the risk of infections in which *S. aureus* is frequently implicated (i.e., skin and soft-tissue infections) is elevated several fold [10].

The nature of our survey limited us in describing the complete clinical context, underlying disease processes, and manifestations of these cases. Also, we did not separately review case records. The cases reported likely represent an underestimate of the total number of cases, because we surveyed a subset of the infectious diseases clinicians in the United States, and other clinicians who treat mycobacterial infections (i.e., pulmonologists) do not participate in the EIN. Alternatively, some of the reported cases might not have met disease criteria [1]. Because of the widespread use of anti-TNF- α compounds, such infections are probably rare, although the lack of a precise denominator for our study prevented us from providing a population-based risk estimate for persons using these medications. Finally, a substantial proportion of patients were treated with other immunosuppressive medications, including corticosteroids, which are known to increase the risk of TB and other infections [11].

In summary, our results suggest that the majority of mycobacterial infections occurring in the context of anti-TNF- α and anti-CD20⁺ B cell therapy in the United States are attributable to nontuberculous mycobacteria and not *M. tuberculosis*. Additional studies are necessary to determine the risks of such complications, and for now, clinicians should remain vigilant for mycobacterial infection and other types of serious infection that occur in patients using these compounds.

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