



## The impact of anti-TNF therapy on the nonspecialist

About 15 years ago, the first anti-tumor necrosis factor (anti-TNF) drugs received approval for treating Crohn disease and rheumatoid arthritis, and a new era of pharmacotherapy was born. A few years before that, I was at a meeting discussing the potential benefits and pitfalls of these new biologic therapies, and I opined that no one would pay for them on an ongoing basis unless they were amazingly effective—which was unlikely, as the drugs only affected a single cytokine. And if they were effective, they would undoubtedly be associated with a host of opportunistic infections. Given my predictive skills, it is no surprise that Warren Buffett rarely calls to ask my opinion.

Clearly, anti-TNF drugs are effective and have raised the bar for how we define successful response to therapy. But recent studies in *early* rheumatoid arthritis indicate that they may not be much better than traditional combination therapy or monotherapy with methotrexate if the methotrexate and the other drugs are given and tolerated at full dose. This is clearly not the case for other inflammatory diseases.

Anti-TNF drugs and other biologics are now part of the arsenal of most medical specialists, so outpatient internists and hospitalists increasingly encounter patients taking these drugs. Since patients with systemic inflammatory disease have an increased prevalence of cardiovascular disease, cardiologists are also seeing more patients taking these drugs. Thus, the overview by Hadam et al in this issue of the *Journal* on the risks of biologic therapies (page 115) is relevant to many readers.

Almost all prescriptions and requests for insurance approval for these drugs are written by subspecialists familiar with their risks. But patients may ask their primary care physicians about the tests and vaccines recommended for those about to start anti-TNF therapy. Before starting anti-TNF therapy, all patients should be tested for previous exposure to tuberculosis and should be treated for latent tuberculosis if appropriate. Blocking TNF leads to a breakdown of the protective granulomatous inflammatory response that contains the mycobacteria and, as with corticosteroid treatment, results in reactivation of the disease. Interestingly, the reactivation is quite often not in the lungs. And since anti-TNF therapy dramatically blunts the inflammatory response, as does corticosteroid therapy, reactivation may appear as nonspecific malaise or may be misinterpreted as a flare in the underlying disease, and thus it may go undiagnosed. Patients should also be screened for exposure to hepatitis B virus. Vaccines, particularly live vaccines, are generally given if possible before starting anti-TNF therapy, and all patients on chronic therapy should get annual influenza vaccines.

Despite initial concerns about a dramatically increased risk of routine and opportunistic infections in patients on anti-TNF therapy, this has not been observed. Even in the perioperative setting, the increased risk of infection is modest. What has struck me, however, is the way these drugs, like steroids, blunt and mask the signs of infection. I have seen deep soft-tissue, intra-abdominal, and native and prosthetic joint infections go unsuspected for days or even weeks in the absence of significant fever, elevation in acute-phase markers, or dramatic local findings. We must be extra vigilant.

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There is a fear of malignancy arising or recurring in patients on anti-TNF therapy. This fear is certainly promoted by the required black-box warning about the risk of lymphoma and other malignancies that these drugs carry. The evidence of a significant increase in risk of malignancies other than hepatosplenic T-cell lymphoma in children and nonmelanoma skin cancers is not strong and is likely slanted by an increased risk of certain malignancies associated with the underlying rheumatic disease and other previous therapies. Nonetheless, I am reluctant to use these drugs in patients with a history of melanoma.

We still have much to learn about these drugs. Why are specific agents more effective in some diseases than others? For example, etanercept treats rheumatoid arthritis but not Crohn disease. Also, we still do not know how they can elicit reversible demyelinating disorders or autoantibodies with or without associated drug-induced lupus syndromes. Even odder is the occurrence of psoriasis induced by anti-TNF drugs, despite their being used to treat psoriasis.

My initial skepticism regarding anti-TNF drugs was unjustified. They are being tested and used successfully in an increasing number of diseases. But we all need to increase our familiarity with their unique risks and somehow find a way to deal with their unique cost.



**BRIAN F. MANDELL, MD, PhD**  
Editor in Chief