Editorial

# Using Vaccine Responses to Plumb the Immunologic Consequences of Tumor Necrosis Factor Blockade with Etanercept

Treatment of debilitating inflammatory diseases of connective tissues often requires the use of potent drugs that have adverse effects on immune function and increase the risk of infections. With drugs such as corticosteroids and methotrexate (MTX), the immunosuppressive effects are potentially dangerous but dosage-dependent, necessitating careful dosage limitation for prolonged treatment. Newer agents that target specific mediators of inflammation, such as tumor necrosis factor (TNF), might have less potential to affect immune functions adversely, but the actual effects must be documented as increasing numbers of patients are being treated for a widening range of conditions.

Determining whether a particular drug or treatment strategy adversely affects immunity is an interesting challenge. Detecting an increased risk of serious infections is the most important and practical endpoint. In the case of TNF blockade using monoclonal antibody to TNF-α (infliximab) or TNF-α-soluble receptor (etanercept), available evidence indicates an increased risk of tuberculosis[1] and other granulomatous infections[2] during treatment. Based on reports to the Adverse Events Reporting System of the US Food and Drug Administration to late 2002, granulomatous infections were reported at rates of about 239 per 100,000 patients treated with infliximab and about 74 per 100,000 patients treated with etanercept[2]. Tuberculosis featured in nearly one-half of reports with both drugs, with candidiasis, coccidioidomycosis, histoplasmosis, listeriosis, and nontuberculous mycobacteria accounting for the remainder. Risk of granulomatous infection was 3.25-fold greater among patients treated with infliximab than among those treated with etanercept. Most infections developed during the first 90 days of treatment, consistent with reactivation of latent infection. Cases of severe pneumococcal pneumonia following treatment with infliximab[3] and a case of fatal pneumococcal sepsis in a patient with rheumatoid arthritis treated with etanercept[4] have been reported. Etanercept treatment has also been complicated by serious infection with *Staphylococcus aureus*[5] and group A streptococcus. It is difficult to determine from such reports if the risk of serious nongranulomatous infection is significantly increased above background and attributable to the TNF-blocking agents. The definitive answer requires measurement of infection risks during treatment of suitably large numbers of patients, in comparison with untreated control subjects. This is not an easy task when treated patients are relatively few and scattered among many clinics and when infection risk is influenced by numerous variables including age, disease severity, concurrent medications, and comorbidities. Nevertheless, treatment study networks are increasingly feasible with electronic communications and are increasingly necessary to fully assess the benefits and risks of expensive treatments for uncommon conditions.

Other methods to assess the effects of treatment on immune function are only indirectly predictive of the consequences. In the case of TNF-blocking agents like etanercept, no major alterations are seen in neutrophil function, phagocytosis, T cell proliferative responses, serum immunoglobulin levels, or delayed-type hypersensitivity reactions[6]. Studies of mice showed that TNF-α is required for the formation and maintenance of granulomas necessary to contain intracellular organisms like tuberculosis and listeria[7]. Infliximab is more potent than etanercept in disrupting granulomas, which may explain its unique effectiveness in the treatment of granulomatous inflammatory diseases such as Crohn colitis, sarcoidosis, and Wegener's granulomatosis, as well as its greater tendency to reactivate latent infections.

An appealing but infrequently used approach to assess immunity is to measure the functional capacity of treated individuals to respond to an antigenic stimulus, as this can mimic pathogen challenge and might predict how adequately a challenge will be met. Since TNF-α participates in activation of T cells during antigen presentation and stimulates B cells[8], it would be relevant to examine the effects of TNF-α blockade on vaccine responsiveness. In this issue of *The Journal*, Mease and colleagues[9] examine pneumococcal vaccine responses in psoriatic arthritis patients treated with etanercept.

In designing a study to assess immune responses using a vaccine antigen, a number of variables must be considered. Administering a new antigen will demonstrate the capacity for a primary response, whereas a familiar antigen will elicit a booster response. Between primary and booster responses, the latter are less likely to be impaired by moderate immunosuppression. Responses to protein antigens are more relevant to viral infections like influenza, whereas responses to polysaccharide antigens are more relevant to bacterial pathogens with surface capsules such as pneumococci. Anti-capsular antibodies are opsonic, promoting uptake of bacteria by phagocytic cells. Responses to polysaccharide antigens involve a unique, T cell-independent response pathway in which specific B cells are stimulated to respond without T cell help. If TNF-$\alpha$ is an important stimulus to T helper cells[8], studying the T-independent pathway may not reveal all of the relevant effects of TNF blockade.

Responses to polysaccharide vaccines are peculiar in several respects. Individuals typically respond to an effective stimulus (vaccine dose) with maximal B cell proliferation and antibody production, according to their genetic capacity[10]. Antibody production diminishes with time in the absence of reexposure. Repeat stimulation causes renewed B cell proliferation and antibody production, to about the levels achieved after initial exposure, although advancing age limits responses. Importantly, a true booster effect as seen with protein antigens is not achieved with polysaccharide antigens. Assessing responses to particular polysaccharide antigens may yield insights that are generalizable to other bacterial polysaccharide antigens (also controlled by the $V_3H$ gene family) but not to protein antigens. Ideally one would examine both T cell-dependent and T-independent response pathways using protein and polysaccharide vaccines.

Assessing responses to pneumococcal polysaccharide vaccine poses some specific challenges. The vaccine contains 23 unique capsular types, so to be practical one must choose a few types for response measurements. Ideally one would select the types that have been associated with infection in patients treated with etanercept, but this information is lacking. Mease, *et al* chose 5 antigens (9V, 14, 18C, 19F, and 23F) for which assays are available because they are contained in new pediatric vaccines, but these types are not necessarily the most frequent causes of infection in adults[11]. However, they are frequent colonizers of the upper airway in early life, so study participants were likely to have developed antibody responses. Since genetics determine if individuals will respond to some, most, or all pneumococcal types examined[10], studies need to include large numbers of subjects to achieve a representative sample. A protective level of serum antibody has not been defined and may differ among serotypes and clinical situations. Antibody avidity also differs among individuals and is not reflected in routine immunoassays. Mease, *et al* chose to examine vaccine responses in terms of fold increases in serum antibody levels between pre- and post-immunization samples, but the lack of a true booster response to pneumococcal antigens may limit the scope of increases to 2-fold or less, especially if antibody levels are relatively high before vaccine administration, as might occur with heightened exposure to TNF-$\alpha$ and other mediators in chronic arthritis. A control group of age-matched adults without arthritis would have been interesting in this respect.

Against this background, Mease, *et al* made a valiant attempt to gather meaningful data. Their study population was reasonably large and well defined, assembled from 17 sites. Treatment group assignments were stratified to account for the effects of MTX treatment, and treatment procedures were indistinguishable between etanercept and placebo recipients. Drug treatment continued for 4 weeks before vaccine was administered, a noteworthy uniformity but possibly too short a time for maximal effects on immune responsiveness. Most subjects had substantial antibody levels to all 5 serotypes prior to immunization and experienced an increase in levels afterward. The pattern of responses was not significantly different between etanercept and placebo-treated groups. The subset treated with MTX responded less well than those not receiving MTX. Older age also reduced response rates.

One can reasonably conclude from this study that 4 weeks of etanercept treatment does not appear to diminish antibody recall responses to the 5 polysaccharide antigens examined. Primary responses were not assessed, as could have been done using a different panel of serotype antigens. Whether responses to immunization were sufficient to protect against the pneumococcal serotypes most likely to cause infection in arthritis patients is unknown. Whether etanercept-treated patients can respond quickly enough to airway colonization with pneumococci to avoid subsequent pneumonia or invasive infection is also unknown, as this scenario was not modeled by the study design. No inferences can be drawn about the effects of etanercept treatment on immune responses to protein antigens and vaccines. MTX treatment significantly reduced responses to immunization in this study and this should serve as a reminder that pneumococcal vaccination is best given before arthritis patients require immunosuppressive medications.

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