Rheumatoid Arthritis and the Incidence of Herpes Zoster: Risky Business

Jeffrey I. Cohen
Medical Virology Section, Laboratory of Clinical Infectious Diseases, National Institutes of Health, Bethesda, Maryland

(See the article by McDonald et al. on pages 1364–71)

Estimates indicate that each year nearly 1 million persons in the United States develop zoster, and more than half are age ≥60 years old [1]. This number is expected to increase as the population ages. The major risk factors for the development of herpes zoster are increased age and impairment of cellular immunity. While antibody responses are important for preventing or attenuating varicella, they do not contribute protection against reactivation of varicella-zoster virus. In contrast, cellular immunity is important for limiting progression of varicella and for preventing zoster. Although antibody responses to varicella-zoster virus are often maintained into old age, cellular immunity declines and the incidence of zoster increases with age. Cellular immunity includes both virus-specific CD4+ memory and CD8+ cytotoxic T cells. Patients receiving immunosuppressive therapy or hematopoietic cell or organ transplants and those with human immunodeficiency virus, hematologic malignancies, systemic lupus erythematosus, or rheumatoid arthritis are at increased risk for developing zoster.

Patients with rheumatoid arthritis have a nearly 2-fold risk of developing infections compared with age- and sex-matched control subjects [2]. The increased rate of infections may be due to immunosuppressive medication used to treat rheumatoid arthritis or to the underlying disease itself. T cells from patients with rheumatoid arthritis show accelerated immunosenescence with reduced diversity, which might contribute to the increased rate of infections [3].

In the study by McDonald et al. [4] in this issue of the journal, the authors report on risk factors for zoster on the basis of a retrospective cohort study of 120,000 patients, encompassing 171,000 patient-years, with rheumatoid arthritis. The incidence of zoster in their patients with rheumatoid arthritis, 9.96 episodes per 1000 years, was similar to that of other studies of patients with rheumatoid arthritis. The incidence of zoster in their patients with rheumatoid arthritis, 9.96 episodes per 1000 years, was similar to that of other studies of patients with rheumatoid arthritis. The incidence of zoster in their patients with rheumatoid arthritis, 9.96 episodes per 1000 years, was similar to that of other studies of patients with rheumatoid arthritis. The incidence of zoster in their patients with rheumatoid arthritis, 9.96 episodes per 1000 years, was similar to that of other studies of patients with rheumatoid arthritis.

The authors compared the risk of zoster in patients receiving different TNF-α inhibitors and found that patients receiving infliximab had a higher rate of zoster than those receiving etanercept or adalimumab. Etanercept is a fusion protein that consists of 2 TNF-α receptor molecules linked to the fragment crystallizable (Fc) domain of human immunoglobulin G1. Infliximab is a chimeric mouse-human anti–TNF-α antibody, but adalimumab is a fully human monoclonal anti–TNF-α antibody. Most studies [5–7] have shown that patients with rheumatoid arthritis who receive TNF-α inhibitors have higher rates of infection compared with those who receive other immunosuppressive medications, especially during the first 6 months of therapy.

Much attention has focused on the increased incidence of mycobacterial and invasive fungal infections in patients receiving TNF-α inhibitors [8]. The rate of reactivation of latent tuberculosis for patients receiving infliximab or adalimumab is estimated to be ~5 times greater than that for patients receiving etanercept.
Strangfeld et al. [9, 10] reported higher rates of herpes simplex and varicella-zoster virus reactivation in patients with rheumatoid arthritis who were receiving infliximab and adalimumab, compared with those who were receiving etanercept. TNF-α inhibitors replicate varicella-zoster virus and synergizes with interferon to inhibit virus growth [11]. TNF-α inhibitors have also been linked with severe disease associated with reactivation of hepatitis B and cytomegalovirus in case reports [12].

Several reasons might explain the higher risk of zoster in patients who received infliximab compared with those who received etanercept in the study by McDonald et al. [4]. First, because infliximab is given intravenously, it reaches peak blood levels that are >20-fold higher and mean serum concentrations that are >5-fold higher than those of etanercept, which is given subcutaneously [13]. Second, infliximab binds to 1 or 2 molecules of monomeric and/or trimeric transmembrane or soluble TNF-α, but etanercept binds only single trimers of transmembrane or soluble TNF-α [14]. Binding of multiple transmembrane TNF-α molecules results in cross-linking and signaling through the cytoplasmic domain of TNF-α, resulting in apoptosis of T cells [15]. Binding multiple molecules of soluble TNF-α leads to the creation of large molecular weight complexes that can inhibit TNF receptor signaling and might result in reduced survival of cells. Third, infliximab induces higher levels of complement-dependent cytotoxicity of T cells than does etanercept [15].

It is somewhat surprising that the rates of zoster were lower in patients receiving adalimumab than in those receiving infliximab in the study by McDonald et al. [4]. Both TNF-α antibodies have similar binding properties to transmembrane and soluble TNF-α compared with etanercept, and both antibodies induce complement-dependent cytotoxicity at similar levels [15] and reduce antigen-induced production of interferon-gamma, compared with etanercept, which has little or no effect in these assays [16]. As noted above [8, 9, studies of patients receiving the 2 monoclonal antibodies had higher rates of reactivation of tuberculosis than those receiving etanercept, and 1 study showed higher rates of herpes simplex and varicella-zoster virus reactivation with the monoclonal antibodies than with etanercept.

Infliximab and adalimumab have 2 important differences that might explain the higher rate of zoster with infliximab, compared with adalimumab. First, infliximab is given intravenously, resulting in high blood levels, but adalimumab is given subcutaneously, with lower peak concentrations [13]. Second, infliximab is a chimeric mouse-human antibody, and 40% of patients who receive infliximab alone develop antichimeric antibodies that can neutralize the activity of infliximab; in contrast, the frequency of antichimeric antibodies is decreased when the drug is given concomitantly with methotrexate [17]. Adalimumab is a fully human antibody and is much less likely to induce neutralizing antibodies. Accordingly, it is recommended that patients with rheumatoid arthritis receive methotrexate concurrently with infliximab but not necessarily with adalimumab. Therefore, in the study by McDonald et al. [4], patients who received infliximab may have had a higher degree of immunosuppression, with an increased risk of reactivating zoster, than those who received adalimumab.

How can knowledge that certain immunosuppressive drugs are more likely to increase the risk of zoster help our patients with rheumatoid arthritis? In 2006, the Food and Drug Administration licensed a live attenuated vaccine to prevent herpes zoster. The vaccine is not contraindicated in persons taking low-dose azathioprine (≤3 mg/kg/d), prednisone (<20 mg/d), or methotrexate (≤0.4 mg/kg/wk) [18]. However, like other live attenuated vaccines [19], zoster vaccine is contraindicated in persons receiving high-dose prednisone or those receiving TNF-α inhibitors [18]. On the basis of the high rates of zoster in persons receiving immunosuppressive therapy, zoster vaccine is recommended for persons ≥60 years old at least 2 weeks (and preferably 1 month) prior to receiving these medications. The mean age of patients receiving TNF-α inhibitors who developed zoster in the study by McDonald et al. [4] was 58.5 years, which is less than the age for which the zoster vaccine is indicated. Thus, a clinical trial should be considered for vaccinating patients with rheumatoid arthritis who are <60 years old and who will soon be receiving TNF-α inhibitors or high doses of prednisone, azathioprine, or methotrexate, to determine if the vaccine reduces the incidence of zoster in these patients.

Acknowledgments


References