

# Rheumatoid arthritis and herpes zoster: risk and prevention in those treated with anti-tumour necrosis factor therapy

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## COMMENTARY

In this issue of *Annals of Rheumatic Diseases*, Garcia-Doval and colleagues add to a flurry of recent studies examining the risk and outcomes of herpes zoster (HZ) among those patients who use anti-tumour necrosis factor (TNF) therapies. While the increased risk of infection due to granulomatous and select other intracellular pathogens has been clearly demonstrated in this setting,<sup>1-3</sup> much less is clear with regard to viral pathogens.<sup>4</sup> The reactivation of varicella zoster virus (HZ or shingles) is of public health concern given HZ's ability to cause substantial long-term pain, depression and disability due to postherpetic neuralgia (PHN).<sup>4,5</sup> HZ is common; approximately one-third of the population will experience it during their lifetime, with 18% of cases resulting in PHN and 10% to 15% involving ocular tissues with potential for permanent visual loss. Rarely, HZ can disseminate and cause systemic complications and death, a risk heightened by HIV infection and other forms of severe immunosuppression.<sup>6,7</sup> HZ rates increase substantially with age, as cell-mediated immunity to varicella virus wanes and as comorbidities associated with immunosuppression become more common. In the USA, HZ incidence rates range between 4 and 11/1000 patient-years in patients aged 50 and 80 years, respectively, with rates higher in women.<sup>6,7</sup>

Recently, a live-attenuated vaccine to prevent HZ (Zostavax, Merck, Whitehouse Station, New Jersey, USA) has been developed and approved for use in patients age 60 years or older, regardless

of their HZ or varicella history.<sup>7</sup> For rheumatologists, who frequently treat immunosuppressed individuals within this age group, the questions begin here: are my patients at increased risk for HZ due to their disease or their therapies? Should I avoid anti-TNF therapies in patients with a history of HZ? Can I vaccinate my patient and when?

## THE RISK OF HZ ASSOCIATED WITH RHEUMATOID ARTHRITIS AND ITS THERAPIES

Garcia-Doval *et al*<sup>8</sup> examined rates of hospitalised episodes of HZ and primary varicella infection within the Spanish BIOBADASER database, a registry of patients with rheumatic disease using biological therapy. They documented 106 cases of HZ among 4655 patients treated with anti-TNF (over 15 000 patient-years of follow-up), for an HZ incidence of 6.5/1000 patient-years in persons using anti-TNF therapy. Of these 106 cases, only 5 required hospitalisation making the rate of hospitalised HZ 32/100 000 patient-years. None of these cases involved disseminated HZ. While rates of hospitalisation in their present study were ninefold higher in patients with rheumatoid arthritis (RA) using anti-TNF therapy as compared to the background Spanish population (they did not compare rates to patients with RA not exposed to biologicals), the authors conclude the absolute risks of hospitalised HZ are so low that, coupled with the risk of vaccine-related serious adverse events, HZ vaccination should not be considered prior to anti-TNF therapy. But is this conclusion justifiable?

In the last 2 years, a number of other large population-based studies have evaluated the relative risks of HZ with anti-TNF and non-biological disease-modifying antirheumatic drug (DMARD) therapy in patients with RA. Smitten *et al*<sup>9</sup> found the overall rate of HZ in patients with RA to be more than

double that of the general population (9.8 vs 3.7/1000 patient-years), and in a nested case-control study found the HZ risk to be slightly elevated in patients with RA using biological DMARDs (OR 1.54) or traditional DMARDs (OR 1.37) compared to no DMARD therapy. Prednisone use had the highest risk estimate (OR 2.51), and its use in conjunction with DMARDs elevated risk beyond that seen with the DMARDs alone. Strangfeld *et al*<sup>10</sup> followed over 5000 patients within the German RABBIT registry and documented 86 HZ episodes for crude incidence rates of 11.1, 8.9 and 5.6 per 1000 patient-years for monoclonal antibody, etanercept and conventional DMARDs, respectively. While a large percentage of these patients were hospitalised (15%), mostly due to multidermatomal disease, only one had disseminated complications. In multivariate analysis, the rate of HZ in monoclonal antibody treated individuals was found significantly elevated (HR 1.82 (1.05–3.15)), while the rate of etanercept associated cases was not statistically significantly elevated. In contrast to the Strangfeld *et al* paper, McDonald and colleagues conducted a large population-based study among 20 000 patients with RA within the US Veteran's Affairs health system. While they found a similar HZ incidence of 10/1000 patient-years and also observed an elevated risk with prednisone use, their results were different for those treated with anti-TNF therapy.<sup>11</sup> Overall, they observed no difference in HZ risk for those treated with anti-TNF therapy from those treated with non-biological DMARDs. Further, within the anti-TNF treated cohort, they documented statistically significant protective associations for etanercept (HR 0.62) and adalimumab (HR 0.53), and a non-significant risk elevation for infliximab (HR 1.32). These investigators also documented a low rate of disseminated complications and hospitalisation for patients treated with anti-TNF who developed HZ during therapy. Lastly, Wolfe *et al*<sup>12</sup> did not find an increase HZ risk with anti-TNF therapy (although they did not design their study to necessarily answer this question) and the authors of the present study from BIOBADASER previously reported elevated (RR 2.7), but not statistically significant, HZ rates of any severity in patients with RA treated with anti-TNF versus non-biological RA comparators.<sup>13</sup>

Collectively, these studies answer some of our questions: yes, HZ risk is

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elevated in RA and it is further elevated 1.5–2.0-fold by prednisone. The inconsistent results for anti-TNF therapy, however, are confusing and in stark contrast to the increased risks observed for anti-TNF therapy with tuberculosis and other granulomatous pathogens, where a mechanism of action has been demonstrated in vitro and in animal models.<sup>14–16</sup> One could hypothesise that TNF antagonist-driven downregulation of interferon could promote varicella reactivation, however a firm hypothesis and experimental evidence are currently lacking. Further, the low rates of disseminated HZ observed among anti-TNF users are worth noting. While this could suggest that TNF blockade does not substantially hinder the host's ability to contain HZ once reactivated, it is likely in most cases anti-TNF therapy was stopped and antiviral therapy was employed.

**SHOULD I VACCINATE MY PATIENT WITH RA PRIOR TO INITIATION WITH ANTI-TNF THERAPY?**

While we agree that the rates of hospitalised and complicated HZ observed in Garcia-Doval *et al's* study were low, we disagree with the author's conclusion regarding vaccination and believe

the rationale for zoster vaccination goes beyond the goal of simply preventing hospitalised HZ. Clinical trials of Zostavax among largely healthy patients 60 years and older suggest the vaccine decreases HZ risk by 51% and PHN by 66% in the 3 years post vaccination.<sup>7 17</sup> Rates of serious adverse events (SAEs) were similar (1.4%) between vaccine and placebo groups in the 38 000 person phase III Shingles Preventions Study. In a safety substudy, SAEs were more likely to occur in the 42 days post vaccination among vaccinated individuals (RR 1.5, (1.0–2.3)), although these events were infrequent (1.9% vaccine vs 1.3% placebo) and rates of hospitalisation and death were not different between vaccine and placebo groups.<sup>7 17</sup>

Presently, there are no prospective data attesting to the efficacy of HZ vaccination in patients with RA specifically. However, strong evidence exists arguing for the protective effect and importance of vaccinating those ≥60 years, and given that patients with RA are at higher risk for HZ and that vaccination with live viruses is contraindicated while using biological therapies, it seems logical to target this group for vaccination before anti-TNF initiation. The intent of vaccination is to lower their risk for 'uncomplicated' HZ and the significant

morbidity associated with this common condition, in addition to the rare but more serious manifestations of HZ. Future studies should aim to further elucidate the potential benefits of vaccinating patients with RA specifically, including those younger than 60 years old and those currently receiving various forms of immunosuppressive therapy (figure 1). Should it be standard of care to consider HZ vaccination in patients with RA age ≥60 years prior to anti-TNF initiation or other long-term immunosuppressive regimens? We believe it should.

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- ▶ For persons on immunosuppressive therapy, including high-dose corticosteroids (≥20 mg/day of prednisone or equivalent) lasting 2 or more weeks, Zoster vaccination should be deferred for at least 1 month after discontinuation of such therapy (209).
- ▶ Short-term corticosteroid therapy (<14 days); low-to-moderate dose (<20 mg/day of prednisone or equivalent); topical (eg, nasal, skin, inhaled); intra-articular, bursal, or tendon injections; or long-term alternate-day treatment with low to moderate doses of short-acting systemic corticosteroids are not considered to be sufficiently immunosuppressive to cause concerns for vaccine safety. Persons receiving this dose or schedule can receive zoster vaccine.
- ▶ herapy with low-doses of methotrexate (≤0.4 mg/kg/week), azathioprine (≤3.0 mg/kg/day), or 6-mercaptopurine (≤1.5 mg/kg/day) for treatment of rheumatoid arthritis, psoriasis, polymyositis, sarcoidosis, inflammatory bowel disease and other conditions are also not considered sufficiently immunosuppressive to create vaccine safety concerns and are not contraindications for administration of zoster vaccine.
- ▶ Persons receiving recombinant human immune mediators and immune modulators, especially the anti-tumor necrosis factor agents adalimumab, infliximab and etanercept. The safety and efficacy of zoster vaccine administered concurrently with these agents is unknown. If it is not possible to administer zoster vaccine to patients before initiation of therapy, physicians should assess the immune status of the recipient on a case-by-case basis to determine the relevant risks and benefits. Otherwise, vaccination with zoster vaccine should be deferred for at least 1 month after discontinuation of such therapy.

**Figure 1** Current Centers for Disease Control (CDC) and Prevention and Advisory Committee on Immunization Practices (ACIP) recommendations for use of the Zostavax for persons using immunosuppressive therapies common in rheumatoid arthritis.<sup>7</sup>

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