Editorial

Further Evidence for Influenza and Pneumococcal Vaccination in Patients Treated with Disease Modifying Antirheumatic Drugs and Anti-Tumor Necrosis Factor Agents

Patients with rheumatoid arthritis (RA) have increased risk of infections including possible vaccine-preventable ones[1,2,3,4,5,6,7]. Susceptibility to infections is considered to be partly associated with RA itself, i.e., immunological alterations as a part of the disease, disease activity, and disability[2,3]. Antirheumatic treatment, in particular longterm use of glucocorticoids, but also traditional disease modifying antirheumatic drugs (DMARD) and biological remedies have all been shown to increase risk of infections[4,5,6]. In addition, higher age, concomitant smoking, common comorbidities such as chronic obstructive pulmonary disease, diabetes mellitus, kidney disease, or malignancies contribute to increased infection risk[2,3,5]. Vaccination is an appealing strategy in the attempt to reduce the burden of infectious diseases in RA. The recent European League Against Rheumatism (EULAR) recommendations, based on current evidence and expert opinion, recommend that rheumatologists strongly consider annual inactive influenza and pneumococcal vaccination for their patients with inflammatory rheumatic diseases[7]. Similarly, the US Centers for Disease Control (CDC) Advisory Committee on Immunization Practices (ACIP) recommends these vaccines to all subjects ≥ 65 years and those treated with immunosuppressive agents[8]. Thus, the majority of patients with RA should get annual seasonal influenza vaccine, and pneumococcal vaccine at least once in life. However, vaccine coverage among patients with RA, including those treated with anti-tumor necrosis factor (TNF) agents is still low[7,8]. There are a number of reasons for low influenza and pneumococcal vaccination rates. Anti-TNF treatments as first biologics for treatment of RA have been available for some 15 years, so data on safety, immunogenicity, and effectiveness of vaccines performed under treatment with these and other biologics are still limited. Prelicensure studies address these issues, but the number of patients included is often limited, and eligibility criteria do not allow inclusion of patients with comorbidities common in daily clinical practice. On the other hand, the number of patients participating in postlicensure studies is often too small to assess the safety of vaccines. This was recently illustrated by cases of narcolepsy among adolescents and younger adults observed first after mass vaccination against pandemic H1N1 influenza[9]. Occasional case reports or smaller case series on increased activity or flare in the existing rheumatic disease, onset of other rheumatic diseases, or onset of other autoimmune diseases after certain vaccinations appear continually in the literature. Those reports often describe a temporal association after certain vaccinations, usually in genetically predisposed individuals[10].

Larger epidemiological studies showing a causal association between vaccination and onset of RA are so far lacking and are very difficult to perform. A case-control study encompassing nearly 2000 incident cases of RA and randomly selected controls matched for age, gender, and residency could not demonstrate an increased risk of RA after previous common vaccinations[11].

Uncertainty regarding a possible impact of the antirheumatic treatment on immunogenicity of vaccines is an additional reason for not encouraging our patients to be vaccinated. A number of studies have investigated antibody response following influenza and pneumococcal vaccination in patients with RA receiving anti-TNF treatments such as etanercept, infliximab, and adalimumab but with somewhat inconsistent results[7]. Data on patients treated with certolizumab pegol (CZP) or biologics with other modes of action, such as rituximab, tocilizumab, or abatacept, are limited[7,12,13,14,15].

In this issue of *The Journal*, Kivitz and coworkers present the results of a randomized, single-blind, multi-

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center, placebo-controlled trial on antibody response to inactivated, trivalent influenza and 23-valent pneumococcal polysaccharide vaccine in CZP-treated patients with RA[16]. Vaccines were administered during the initial, uploading dose of CZP, and antibody levels were measured 4 weeks after vaccination. Compared to placebo CZP treatment did not significantly impair the ability to mount antibody response to any of the vaccines.

There is growing evidence that anti-TNF treatment may influence B cell response to antigen challenge. T cell-dependent antibody response seems to be predominantly affected[17]. The exact mechanisms by which these remedies influence the T cell-dependent response are not entirely elucidated, and more experimental studies are needed. Recently, a study investigating the effect of anti-TNF treatment on B cell activation and the maturation of antibody responses after vaccination found severely impaired primary T cell-dependent antibody response (after vaccination against hepatitis), and only moderately decreased T cell-independent antibody response (after pneumococcal vaccination) in patients with arthritis[17]. *In vitro* and *ex vivo* analyses did not identify any general B or T cell defect. The authors conclude that these findings indicate a more selective disturbance of the germinal center being responsible for impaired T cell dependent response.

Kivitz, *et al* report that 50.5% of CZP-treated patients, including those who already had protective antibody levels before vaccination, mounted satisfactory antibody levels (compared to 54% of placebo-treated patients) 4 weeks after influenza vaccination. Apparently, the ability of protein antigens to induce antibody response was maintained during the early, loading treatment period. Similar results have been reported in other studies investigating immunogenicity of influenza vaccine in patients treated with other anti-TNF agents[7,13,15]. Given the fact that influenza vaccine often contains some virus strains included in the previous season's vaccine, seasonal influenza vaccination may result in boosting antibody response rather than achieving primary response. This may have contributed to a better overall antibody response.

Compared to protein antigens, polysaccharides are generally considered as poorly immunogenic. However, Kivitz, *et al* report satisfactory antibody response to 23-valent pneumococcal polysaccharide vaccine in 53% of all CZP treated patients, including patients with protective prevaccination antibody levels[16]. In the placebo-treated patients the figure was 58%. Thus ongoing CZP treatment does not seem to significantly disturb T-cell independent antibody response to polysaccharide antigen challenge, which is in line with aforementioned experimental data[17].

Concomitant methotrexate treatment was found to impair antibody response to both vaccinations, as reported by others[12,14,15]. The mechanisms are not known in detail but seem to involve both T cell-dependent and T cell-independent antibody response.

Kivitz, *et al* did not find any significant effect of concomitant glucocorticoid treatment on antibody responses. Patients on prednisolone in doses ≤ 10 mg daily were eligible for the study, and possible association between higher doses and insufficient antibody response could not be ruled out. Since the usage of glucocorticoids is known to be a predictor of infections in RA, this good vaccine response under low-dose glucocorticoids should further encourage rheumatologists in recommending vaccinations to their patients[2,4,5].

Another important issue is the timing of vaccination. Kivitz, *et al* reported antibody response in patients immunized during initiation of the treatment when CZP was given in a loading dose. This illustrates that sufficient antibody response for both vaccinations can be performed under ongoing treatment with anti-TNF agent as reported by others[7]. Whether CZP exhibits a negative impact on these responses during maintenance doses remains to be addressed in future studies. On the other hand, patients about to start methotrexate or rituximab could gain better antibody response and probably better protection against infection if they are immunized before initiation of treatment. However, since some patients respond sufficiently while taking methotrexate, ongoing treatment should not be considered a contraindication for vaccination. Discontinuation of treatment in order to perform vaccinations does not appear to be necessary, but has not been formally studied[7].

Kivitz, *et al* used 23-valent pneumococcal polysaccharide vaccine, which has been available since the early 1980s. The immunogenicity of that vaccine has been a subject of debate, and conflicting results among adults, elderly, and patients with chronic diseases, including immune deficiencies, have been observed[18]. According to the latest metaanalysis from Moberley, *et al* there is evidence of vaccine efficacy against invasive pneumococcal disease in healthy adults, but not against all-cause pneumonia in high-income countries in the general adult population, nor among patients with chronic illness[18]. The CDC ACIP currently recommends the use of both 13-valent pneumococcal conjugate vaccine and 23-valent polysaccharide vaccine to adults aged ≥ 19 years with immunocompromising conditions; preferably the conjugate vaccine is administered first, followed by the polysaccharide one[8]. The advantage of that vaccination strategy in patients with inflammatory rheumatic disease needs to be investigated.

One has to keep in mind that antibody response is a surrogate measure of vaccine efficacy. Although the association between good antibody response and protection against infection is shown[19], we need studies investigating whether vaccinations performed during ongoing treatment with biologics really provide protection against infections.

A few studies have reported that vaccination actually is associated with lower occurrence of infection[20,21]. One suggests the effectiveness of seasonal influenza vaccine[19]; the other, protection against pneumococcal pneumonia up to 10 years following a single dose of 23-valent pneumococcal polysaccharide vaccine in methotrexate treated patients with RA[21].

While awaiting results from several such studies, there is more work to do on implementation of recommendations on vaccinations among patients with inflammatory rheumatic diseases. Overall, our patients see their rheumatologist more often than their primary care physician, which gives us the opportunity to inform, educate, and encourage our patients to be vaccinated. Having experience in and knowledge of DMARD/biological treatment, rheumatologists should also provide specific advice on appropriate vaccinations to primary care and other healthcare providers.

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