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Vaccinations for Rheumatoid Arthritis

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Abstract Patients with rheumatoid arthritis (RA) suffer an increased burden of infectious disease-related morbidity and mortality and have twice the risk of acquiring a severe infection compared to the general population. This increased risk is not only a result of the autoimmune disease but is also attributed to the immunosuppressive therapies that are commonly used in this patient population. Given the increase in infection-related risks in RA, there is great interest in mitigating such risk. A number of vaccines are available to the rheumatologist, with a handful that are of importance for RA patients in the United States. The goal of this paper is to highlight the most recent literature on the key vaccines and the specific considerations for the rheumatologist and their RA patients, with a particular focus on influenza, pneumococcal, and herpes zoster vaccines. It is important for rheumatologist to understand and be aware of which vaccines are live and what potential contraindications exist for giving vaccines to RA patients.

Keywords Vaccination · Rheumatoid arthritis · RA · Influenza · Pneumococcal vaccination · Herpes zoster vaccination · Biologics · DMARDs

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Rationale for Vaccination: Infection Risk in Rheumatoid Arthritis

Rheumatoid arthritis (RA) patients have an increased burden of infectious disease- related morbidity and mortality and may have up to twice the risk of acquiring a severe infection than patients in the general population. In particular, patients with RA have been shown to have a 1.5- to 2-fold higher risk of being hospitalized for infection, and the risk of death from infection is greater than patients without RA of similar age [1]. This increased risk is not only a result of the autoimmune disease but is also attributed to the immunosuppressive therapies (e.g., glucocorticoids) that are commonly used in this patient population. The respiratory tract, joints, bone, skin and soft tissue are sites that are frequently involved in infectious processes in patients with RA [2, 3]. Long-term prednisone use is associated with a dose-dependent increase in infection, with some studies suggesting increased risk even at "low-dose" prednisone of 5 mg/day [4]. The addition of biologics to DMARDs may amplify the immunosuppressive effects of traditional DMARDs. Moreover, lymphopenia as a result of RA treatment may be an additional risk factor for infection [5].

Current Vaccine Recommendations in Rheumatology

Given the above increase in infection-related risks in RA, there is great interest in prevention of infection. A number of vaccines are available to the rheumatologist, and several are of high importance for RA patients in the United States. It is important for rheumatologist to understand and be aware of which vaccines are live and what potential contraindications exist for giving vaccines to an immunosuppressed patient population. Both the American College of Rheumatology (ACR) and the European Union League against Rheumatism (EULAR) have issued recommendations about appropriate use of vaccines for RA patients.

The 2012 ACR vaccine recommendations (Table 1) state that the optimal time for administering vaccines (e.g., influenza, pneumococcal, HPV, others) is prior to starting a non-biologic or biologic DMARD [6]. In general, this helps optimize host vaccine responses, and, in the case of live vaccines like herpes zoster vaccine, limits the theoretical risk of local or disseminated infection in an immunosuppressed patients taking a biologic [6]. More detailed information about each of the vaccinations most relevant for adult RA patients in the U.S. are described in this review, with a particular focus on the extent to which biologics and non-biologic DMARDs could affect vaccine effectiveness.

Key Vaccines and Specific Considerations for Rheumatologist and their RA Patients

Influenza

Overview and Recommendations

The constituents of the seasonal influenza vaccine potentially change on a yearly basis according to surveillance data regarding the most prevalent circulating influenza strain. Starting in 2009, the pandemic H1N1 strain was incorporated into the basic constituents of the trivalent seasonal vaccine; two influenza A antigens along with an influenza B component(s). In the United States, as of 2013, a quadravalent and trivalent vaccine became available in killed formulations (intramuscular) and the trivalent vaccine is also available as a live formulation (nasal). It is anticipated that the quadrivalent will gradually replace the trivalent vaccine in the next few years. The live vaccine is approved in only healthy individuals aged 2–49 years and is contraindicated for those with rheumatic disease [7, 8]. For the treating rheumatologist, only intramuscular attenuated influenza vaccine formulations should be administered on an annual basis [6, 8]. In patients with an anaphylactic reaction to eggs, a recombinant influenza vaccine is available and can be used as it lacks ovalbulmin [8].

Effect of DMARDs and Biologics on Vaccine Effectiveness

A total of 16 studies in RA have been published that describe use of the influenza vaccine and its immunologic effectiveness, with the potential for heterogeneity noted given that the serotypes covered can vary from year to year. Influenza vaccine studies within this population typically focus on the

Table 1 2012 ACR recommendations regarding the use of vaccines in patients with RA starting or currently receiving DMARDs or biologic agents[a]

	Killed vaccines			Recombinant vaccine	Live attenuated vaccine
	Pneumococcal[b]	Influenza (intramuscular)	Hepatitis B[c]	Human papillomavirus	Herpes zoster
Before initiating theraphy					
DMARD monotheraphy	✓	✓	✓	✓	✓
Combination DMARDs[d]	✓	✓	✓	✓	✓
Anti-TNF biologics[e]	✓	✓	✓	✓	✓
Non-TNF biologics[f]	✓	✓	✓	✓	✓
While already taking theraphy					
DMARD monotherapy	✓	✓	✓	✓	✓
Combination DMARDs	✓	✓	✓	✓	✓
Anti TNF biologics[e]	✓	✓	✓	✓	Not recommended[h]
Non-TNF biologics[g]	✓	✓	✓	✓	Not recommended[h]

DMARDs disease-modifying antirheumatic drugs; ✓ recommend vaccination when indicated (based on age and risk); *anti-TNF* anti-tumor necrosis factor

[a] Evidence level was C for all of the vaccination recommendations. For definitions and key terms, please refer to Table 2

[b] The Centers for Disease Control and Prevention also recommends a one-time pneumococcal revaccination after 5 years for persons with chronic conditions such as rheumatoid arthritis (RA). For persons ages ≥65 years, one-time pneumococcal revaccination is recommended if they were vaccinated ≥5 years previously and were age <65 years at the time of the primary vaccination

[c] If hepatitis risk factors are present (e.g., intravenous drug abuse, multiple sex partners in the previous 6 months, health care personnel)

[d] DMARDs include hydroxychloroquine, leflunomide, methotrexate, minocycline, and sulfasalazine (listed alphabetically) and combination DMARD therapy included double (most methotrexate based. with few exceptions) or triple therapy (hydroxychloroquine + methotrexate + sulfasalazine)

[f] Anti-TNF biologics included adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab (listed alphabetically)

[g] Non-TNF biologics included abatacept, rituximab, and tocilizumab (listed alphabetically)

[h] According to the RAND/UCLA Appropriateness Method, panel members judge it as "not appropriate" and therefore it qualifies as "recommended" (median score on appropriates scale was 1)

immunogenicity of the vaccine as a proxy for clinical effectiveness by evaluating surrogate measures of protection such as the geometric mean titer (GMT) of hemaglutinin inhibition (HI) antibodies. HI titers of 1:40 or greater have been shown to be protective against influenza in the general population [9]. Most of the studies evaluated suggest that RA patients using methotrexate and/or anti-TNF therapy (adalimumab, etanercept, infliximab) achieve an acceptable humoral response, although their response is lower than in healthy controls [10•, 11, 12•, 13–18]. A recent study, in 2012, involving RA patients receiving tocilizumab, methotrexate (MTX) or the combination of the two suggest that there was no decreased effects of TCZ, and post-vaccination GMTs increased significantly for all strains of the influenza vaccine [19•]. Abatacept, on the other hand, has been shown to significantly reduce the humoral response to pandemic 2009 influenza A/H1N1 vaccine in RA patients compared to patients with RA on methotrexate and healthy controls, although this study did not evaluate tri- or quadrivalent vaccine [12•, 20]. Rituximab severely reduces the responsiveness of the influenza vaccine in patients with RA as shown in several studies, and, not surprisingly, this reduction in response is dependent upon the timing of the vaccine in relation to rituximab administration [21, 22•, 23, 24]. Supporting data for this assertion includes one study showing that pre-rituximab treated patients had a greater response to the influenza vaccine than those in the post-rituximab treatment group [22•], while another study showed that patients vaccinated 6–10 months after rituximab had a better response that those vaccinated 4–8 weeks after rituximab [23]. It was also found that there was no difference in the levels of vaccine-specific Ig between patients treated with rituximab once as compared with those who were treated more than once, suggesting that repeated courses of rituximab induced no cumulative impairment of the vaccine specific response [22•].

Summary & Recommendation

In summary, the timing of administering the influenza vaccine among patients on immunomodulatory drugs should be straightforward, in that each patient should be vaccinated each fall prior to the advent of the influenza season regardless of their current immunosuppressive regiments, except for rituximab users who were recently treated. For rituxan-treated individuals, waiting as long as possible after treatment would be of benefit, such that clinicians should monitor and be aware of local trends in influenza epidemiology in order to facilitate such decision making. Responses to the influenza vaccine, for the most part, should be adequate no matter what DMARD or biologic regimen is used, except that rituximab severely restricts humoral response to influenza (and other vaccines) when vaccination is given soon after rituximab administration [21, 22•, 23, 24].

Pneumococcal Vaccination

Overview

The pneumococcal vaccine comes in different formulations, polysaccharide or conjugate. The polysaccharide vaccination (PPSV-23) has been used in adults to provide protection against 23 serotypes of *S. pneumonia*, while, in children, the protein conjugate vaccines prevnar-7 and more recently prevnar-13 (PCV-13) are standard of care. Conjugate vaccines typically provide more robust immune responses than do polysaccharide vaccines. Accordingly, more recently, prevnar-13 has been recommended by the Center for Disease Control (CDC) for use in adult immunosuppressed populations due to its theoretical ability to provide a more robust anti-pneumococcal serotype-specific antibody responses to the 12 serotypes shared between PCV-13 and PPSV-23. To date, however, there is a lack of data evaluating PCV-13 responses in patients on immunomodulatory drugs, and it is not yet clear if the conjugate vaccine provides a better response or protection.

Effect of DMARDs and Biologics on Vaccine Effectiveness

Seven studies have evaluated the immune responses of PCV-7 or PPSV-23 in RA patients using DMARDs [17, 25–29, 30•]. Kapetanovic et al. evaluated the immune responses of PCV-7 and PPSV-23 in RA patients based upon biologic use (adalimumab, etanercept, infliximab). Responses were higher for those using TNF blockers in the absence of MTX as compared to those using MTX alone or with TNF blockers. In no category of patient, however, were conjugate vaccine responses with PCV-7 better than those observed for PPSV-23 [26] . The other studies that assess PPSV-23 in the RA population show a diminished response to the vaccine compared to healthy controls, particularly in those using methotrexate. Most studies suggest that the addition of a biologic to MTX does not appear to further diminish the response to the vaccine [17, 25, 27–29]. Despite these studies, the relative clinical effectiveness of either conjugate or polysaccharide pneumococcal vaccines in the setting of patients on immunomodulatory drugs is unknown, and it is possible that one confers better long-term protection than the other despite similar short-term immune responses measured after vaccination. A recent study in 2014 by Bingham et al. evaluated the effect of TCZ on the humoral response to the PPSV-23 vaccine in patients with RA. It showed that 8 weeks after receiving the vaccine, patients on TCZ and MTX had a 60 % response to ≥6 PPVS23 serotypes and 71 % responded that were on MTX alone. The data were insufficient to detect any differences in the treatments [30•]. Another recent study in 2012 by Mori et al. evaluated PPSV-23 in patients with RA on TCZ to assess the impact

of TCZ on antibody response following vaccine administration. The study looked at the GMC of antibodies for serotypes 6B and 23F 4–6 weeks post-vaccination and found that both serotypes increased significantly and were comparable to the control group [19•]. The last two studies were published in 2010 and evaluated the cellular and humoral response to PPSV-23 in RA patients on rituximab. It found that patients that were vaccinated prior to receiving rituximab had a greater response than those vaccinated after rituximab treatment. Like for influenza, it showed that patients treated with rituximab once versus repeated courses induced no further impairment of the vaccine response [22•, 31].

Summary and Recommendations

The pneumococcal vaccine (PPSV-23) is recommended in immunosuppressed patients and should be repeated 5 years after the first vaccination. After this time point, the rationale for giving additional vaccinations is unclear, as diminished immune responses have been documented with additional vaccinations in some patients, for reasons that are unclear [32•]. Recent data suggest that more robust responses to the PPSV-23 vaccine might be observed if the vaccine is given after an initial vaccination with PCV-13 [33•]. This data forms the basis for the recent ACIP recommendations for pneumococcal vaccination in immunosuppressed adult populations (Table 2) [34]. These recommendations are new, however, based upon limited data, and do not include representation of RA patients or those on immunomodulatory drugs.

Table 2 Summary of ACIP Recommendations for pneumococcal vaccines in adult patients with an immunocompromising condition such as rheumatoid arthritis[a]

Prior PPSV-23 Vaccination	Recommendation
None	Give PCV-13 followed by PPSV-23 (at least 8 weeks later) 5 years later, give a booster PPSV-23
One prior PPSV-23	Give PCV-13 (>1 year from PPSV-23) Give booster PPSV-23 (5 years after the last PPSV-23)
Two prior doses of PPSV-23	If >1 year from last PPSV-23, then give PCV-13 Patients who are under age 65 are eligible to receive one further PPSV-23 after turning 65 years old.

[a] Adapted from the CDC. Use of 13-Valent Pneumococcal Conjugate Vaccine and 23-Valent Pneumococcal Polysaccharide Vaccine for Adults with Immunocompromising Conditions: Recommendations of the Advisory Committee on Immunization Practices (ACIP)

Herpes Zoster Vaccination

Overview and Recommendations

In order to prevent herpes zoster (HZ), a live-attenuated vaccine (Zostavax) has been developed and is approved for use in individuals age 50 years or older, regardless of varicella history or previous HZ [35]. Currently, the CDC recommends and the ACR endorses that anyone age 60 and older to become vaccinated against HZ [6, 36]. Despite appreciable efficacy in individuals age 50–59, the reasons for the differences between the indication for age 50 and above and the recommendation starting only at age 60 may be related to the greater population health benefit (based upon greater absolute risk reduction) and associated higher cost-effectiveness in older patients. The ACIP and ACR guidelines currently recommend that patients who use methotrexate (<0.4 mg/kg/week, e.g., 25 mg/week), low to moderate doses of glucocorticoids (<20 mg/day prednisone or equivalent) or short-term corticosteroids (<14 days) or intra-articular, bursal, or tenton corticosteroid injections, or azathioprine (<3.0 mg/kg/day) or 6-mercaptopurine (<1.5 mg/kg/day) can receive this vaccination safely [36]. According to ACIP, the HZ vaccine is contraindicated in patients receiving such medications due to theoretical concerns regarding the safety of live vaccine use in patients using biologic therapies such as anti-TNF therapy. Despite the demonstrated efficacy and safety of the zoster vaccine observed in non-RA patients, there are no prospective trials critically examining the clinical efficacy or safety of HZ vaccination in RA patients.

Effect of DMARDs and Biologics on Vaccine Effectiveness

Despite the dearth of prospective trial data of the zoster vaccine in RA, several population-based observational studies have been conducted examining use of the zoster vaccine in patients with RA and other rheumatic diseases (e.g., spondyloarthropathies) [37]. Among a total of 19,326 RA patients older than age 50, only 206 (1 %) received zoster vaccine, suggesting that clinicians may be uncomfortable using the vaccine in patients with rheumatic diseases. Additionally, approximately 60 vaccinated patients in this study were using anti-TNF therapies within 1 month of vaccination, and no cases of HZ were reported during this time frame. A larger study conducted among Medicare beneficiaries in the US identified a larger cohort of patients (n=663) who has been vaccinated while using biologic therapy (most using anti-TNF therapy, predominantly infliximab) and no patients developed zoster or other varicella disease in the 6 weeks after vaccination [38•]. Within this study, only 3.3 % of RA patients, all of whom were age ≥60, received vaccination suggesting this group remains an important target for HZ prevention via vaccination. Moreover, the study

suggested a clinical effectiveness and an absolute risk reduction for the vaccine similar to that seen for older patients within the Shingles Prevention Study [39].

Summary and Recommendations

Although prospective trial data with the live zoster vaccine is essentially non-existent at the present time, a few observational studies shine a positive light towards the future use of HZ vaccine in an RA patient population. The vaccine should be strongly considered for individuals age 50 and older [40]. Given the high risk of HZ in the RA population, approximately double that of healthy older individuals [41•], it may be warranted to prospectively evaluate the safety and clinical effectiveness of this vaccine in patients using biologic therapy. Additionally, a number of important questions remain about the vaccine, as described below.

Discussion and Evidence Gaps

Recommendations from both the ACR and EULAR highlight the importance and need for vaccination in patients with RA. A number of evidence gaps exist for each of the three major vaccines. For example, the clinical effectiveness of any of these vaccines in an RA population has not been shown prospectively via a controlled trial, and observational data are similarly lacking. In particular, the safety of the herpes zoster vaccine needs to be demonstrated, especially given evidence that patients with RA have high rates of zoster. Additionally, the need for and optimal re-vaccination intervals for pneumococcal vaccination and zoster vaccination is not clear. For example, studies of zoster vaccination conducted in healthy older adults suggest that immunity lasts for up to 5 years [42], but it is unknown whether this finding can be generalized to RA patients.

Finally, despite the availability of these several vaccines, the most effective mechanisms to ensure that at-risk patients receive them have yet to be elucidated. Numerous studies have shown that patients do not receive vaccines as recommended [43]. Despite multiple guidelines, vaccination in the clinical setting is erratic and the need for early efforts through reminder systems such as point of care reminders (paper or electronic medical records) or other health system-related triggers are in their infancy [44]. Another approach would be to delegate a responsible provider or non-physician provider to administer and record all vaccines [45, 46]. More direct engagement of patients, rather than solely relying on their healthcare providers, may be fruitful to improve rates of vaccination. For example, immunization pharmacies in all 50 U.S. states allow patients to receive immunizations without a physician's order or prescription [47], enabling patients to have much more autonomy in receiving vaccination than ever before. While such efforts might improve vaccination use for the general population, the relative timing and contraindications of some vaccines during some types of DMARD and biologic therapies argue for the involvement of the rheumatologist in guiding such decisions.

In conclusion, vaccination remains an important strategy for infection-related risk reduction in rheumatology patients, many of whom are at higher risk for vaccine-preventable infections. RA patients should receive annual influenza vaccine, as well as pneumococcal vaccination in accordance to new guidance from the CDC. While zoster vaccination contains live virus, and it is contraindicated during biologic therapy, the high rates of zoster among RA and other subsets of rheumatology patients raises the importance of greater frequency of use of this vaccine prior to biologic therapy initiation. Further research should aim to evaluate the safety and effectiveness of this and other vaccines specifically within the RA setting.

Compliance with Ethics Guidelines

Conflict of Interest Lisa Perry declares that she has no conflict of interest. Kevin Winthrop declares that he received a grant from Pfizer, consulting for Abbvie, Pfizer, UCB, Genentech. Jeffrey Curtis declares that he received consulting fees and research grants from Amgen, Abbott, BMS, Pfizer, Eli Lilly, Janssen, UCB, Roche/Genentech and CORRONA, and that he receives support from the NIH (AR064172). The authors jointly declare that this work was supported by the Agency for Healthcare Research and Quality (AHRQ) (R01HS018517).

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