Vaccinations in Patients with Rheumatic Disease

Consider Disease and Therapy

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KEYWORDS

• Rheumatic diseases • Immunosuppression • Vaccine • Immunogenicity • Biologics • DMARD • Infection

KEY POINTS

- Influenza vaccine immunogenicity is reduced by rituximab and methotrexate.
- Pneumococcal vaccine immunogenicity is reduced by rituximab, methotrexate, and possibly abatacept and tofacitinib.
- When possible, for patients receiving treatment with rituximab, administration of influenza and pneumococcal vaccines should be administered 6 months after and 4 weeks prior to the next rituximab dose to maximize immunogenicity.
- Live vaccines are contraindicated in the setting of biologic therapy but can be considered in the setting of lower-dose immunosuppression.
- The recombinant herpes zoster vaccine has not been heavily studied in patients with rheumatic diseases; however, it should be recommended with informed decision making.

INTRODUCTION

Risk of infection is increased in patients with rheumatic diseases secondary to both their underlying disease states as well as from immunosuppressive medications used for their treatment. There are many unique aspects of vaccinology in rheumatology patients, including the particular infectious morbidity in this patient population, and perhaps most importantly the impact of conventional synthetic and biologic disease-modifying antirheumatic drugs (DMARDs) on vaccine safety and efficacy. The introduction of biologic therapies has revolutionized the treatment of rheumatic diseases, yet accompanying this is a further increased risk of infection, highlighting the importance of vaccines even further. When considering vaccinating rheumatic diseases patients, disease activity, type of immunosuppression, and timing of vaccine

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administration must be considered to optimize both efficacy and safety. Although it is mainly the rheumatologist's role to keep up to date with vaccine administration and recommendations, awareness and communication with other specialists as well as primary care providers and internists are key, because ultimately it is a group effort. Although it is well-known that vaccines are the best mode of infection prevention, their uptake remains low in patients with rheumatic diseases. The objective of this review is to summarize the impact of immunosuppressive therapies and rheumatic disease on vaccine efficacy in this unique patient population and to present best practices.

GENERAL PRINCIPLES AND RECOMMENDATIONS

The recommended adult immunization schedule is updated annually by the Advisory Committee on Immunization Practices (ACIP) and includes recommendations for immunizing against more than 10 vaccine-preventable infections. The recommendations are stratified by patient population, and under each vaccine recommendation are bullet point recommendations for special situations, which include immunocompromising conditions, for example, patients with rheumatic diseases receiving immunosuppression. The major rheumatology societies have released guidelines as well, some of which are outdated and are discussed later, with the 3 most important vaccines to consider in patients with rheumatic diseases highlighted: influenza, the pneumococcal series, and herpes zoster (HZ).

Vaccination Against Influenza

The American College of Rheumatology (ACR) has published immunization recommendations for patients with rheumatoid arthritis (RA) only and supports universal immunization against seasonal influenza,[1] whereas the European League Against Rheumatism (EULAR) recommendations encourage influenza vaccination be considered for the majority of patients with rheumatic diseases,[2] which is reflective of differing immunization practices between the United States and European countries.

Seasonal influenza vaccine should be administered to all rheumatic disease patients on a yearly basis. Not only are patients with rheumatic diseases at higher risk of contracting influenza compared with the general population,[3] but also they suffer from greater morbidity and exhibit prolonged viral shedding,[4] and influenza vaccination is associated with reduced risk of morbidity and mortality in this population.[5] Patients ages 65 or older should receive a high-dose formulation, which aligns with the ACIP recommendations, where clinical studies have shown variable clinical and cost effectiveness (approximately $20 for standard dose vaccines vs approximately $50 dollars for high dose, without insurance, per Centers for Diseases Control and Prevention [CDC] 2020).[6] A randomized controlled trial assessed antibody responses to a standard-dose quadrivalent influenza vaccine compared with a high-dose trivalent inactivated formulation (HD-TIV) in patients with RA of mean age 61 years and found that those who received HD-TIV achieved superior immunogenicity.[7] High-dose influenza vaccine also has been shown to improve immunogenicity in solid organ transplant patients compared with standard dose.[8] Although there currently is no formal recommendation to administer high-dose influenza vaccines to rheumatic disease patients less than 50 years of age, these findings should be taken into consideration and prompt further studies, because they may be practice-changing.

Pneumococcal

Streptococcus pneumoniae is the leading cause of community-acquired pneumonia, and invasive disease is associated with a high mortality rate in the general

population; this rate is even higher in patients with rheumatic diseases.[9] In the United States, pneumococcal vaccines are available as a 13-valent pneumococcal conjugate vaccine (PCV13) and a 23-valent pneumococcal polysaccharide vaccine (PPSV23). ACIP recommends the prime-boost vaccine strategy for pneumococcal vaccine series in immunocompromised patients, which includes a dose of PCV13 followed at least 8 weeks later by PPSV23, because this sequence has been shown to enhance antibody response compared with a single dose of PCV13 in patients with rheumatic diseases.[10] This strategy is included in the recommendations by the ACR, EULAR, and the European Society of Clinical Microbiology and Infectious Diseases. There are some nuances to this strategy, including specific recommendations for patients who have received PPSV23 prior to PCV13 (**Table 1**), often leading to patients with rheumatic diseases receiving the series incompletely. Despite these nuances, the prime-boost pneumococcal vaccine series should be given to all rheumatic disease patients contemplating starting or already on immunosuppressive medications.

Herpes Zoster

In immunocompetent persons, HZ is a common condition with incidence increasing significantly with age and is associated with substantial morbidity, including painful postherpetic neuralgia, among other complications. Vaccination against HZ is recommended for persons ages 50 and older. In patients with autoimmune and inflammatory diseases, the incidence of HZ is significantly higher, due to both underlying disease and immunosuppressive medications.[11] There are 2 available vaccines against HZ, the live zoster vaccine (LZV) and the recombinant zoster vaccine (RZV). RZV is a nonlive recombinant subunit vaccine with a novel potent adjuvant, Food and Drug Administration (FDA)-approved in 2017, and now is the preferred HZ vaccine by ACIP. Rheumatology society recommendations are outdated, with the ACR recommending LZV be given prior to biologic therapy or tofacitinib for patients ages greater than or equal to 50 years, and EULAR encouraging rheumatologists to consider LZV administration in mildly immunosuppressed patients on a case-by-case basis, which often leaves providers unclear regarding best practices.

The clinical trials that led to RZV approval excluded patients with autoimmune diseases and patients receiving immunosuppressive medications; thus, administering RZV to rheumatic disease patients remains an area of uncertainty due to theoretic concern for disease flare and increased risk of injection site reactions and systemic symptoms as a result of the potent adjuvant used in the vaccine.[12,13] Given the increased incidence of HZ and its complications (including stroke[14]) and an increasing amount of evidence and clinical experience demonstrating acceptable safety of RZV in rheumatic disease patients,[15] RZV should be considered in rheumatic disease patients ages greater than or equal to 50 years, especially in patients receiving treatment with Janus kinase (JAK) inhibitors, where the risk is significantly higher compared with those treated with other biologic disease-modifying drugs.[16]

Herpes Papillomavirus

Human papillomavirus vaccine (HPV). is the most common sexually transmitted infection in the United States and is associated with cervical, vulvar, and vaginal cancer in women, penile cancer in men, and anal and oropharyngeal cancer in both men and women.[17] There is no treatment of HPV infection, further emphasizing the importance of this vaccine. ACIP recommends 3 vaccination with a 2-dose series for ages 9 through 14, and a 3-dose series if initiated between ages 15 years through 26 years;

Table 1
Important vaccines for patients with rheumatic diseases and considerations for administration

Vaccine	Indications for Rheumatic Disease Patients	Contraindications/ Considerations
Influenza		
Numerous inactivated formulations	• Yearly inactivated vaccine recommended for all patients • Patients ≥65 y should receive high-dose vaccine	Rituximab: ideally administer before start of therapy or as long after the first dose and 4 weeks prior to next dose, if possible. Methotrexate: consider holding 2 doses after vaccine administration, in inflammatory arthritis patients with quiescent disease
Live intranasal vaccine		Contraindicated in the setting of CDC recommended immunosuppressive thresholds (see **Box 1**)
Pneumococcal		
PPSV23	Prime-boost series recommended for all patients on immunosuppression: • Vaccine-naïve: PCV13 followed by PPSV23 ≥8 wk later • If <65 y at the start of series, repeat PPSV23 after 5 y. • All patients should receive a final dose of PPSV23 after age 65. • Previously vaccinated with PPSV23: PCV13 ≥ 1 y after PPSV23 • Patients need only 1 PCV13 in a lifetime.	Rituximab and methotrexate: administer before start of therapy, when possible.
PCV13		Efficacy may be reduced by abatacept and tofacitinib.
Herpes Zoster		
LZV	• ACR recommends LZV be given prior to biologic therapy or tofacitinib for RA patients ≥50 y. • EULAR recommends considering LZV administration in mildly immunosuppressed patients on a case-by-case basis.	Contraindicated in the setting of CDC-recommended immunosuppressive thresholds (see **Box 1**)

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Table 1
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Vaccine	Indications for Rheumatic Disease Patients	Contraindications/ Considerations
RZV	• No formal recommendations for administration	In light of an increasing amount of safety data, RZV should be recommended to patients with quiescent rheumatic disease, with informed decision making.
HPV		
9-valent formulation	• ACIP recommends 2-dose series for ages 9–14, and 3-dose series if initiated between 15–26; consider vaccinated ages 27–45 if not vaccinated previously. • 3-dose series recommended regardless of age in immunocompromised persons	Of particular importance in SLE patients

however, the 3-dose series is recommended regardless of age for immunocompromised persons.[18] HPV is of particular importance in patients with systemic lupus erythematosus (SLE), because this patient population experiences a higher incidence of HPV infection, are infected with more often high-risk subtypes, and are less likely to clear infection spontaneously, thus leading to higher rates of cervical and other cancers.[19] ACIP recommendations have been updated to include considering vaccinating adults ages 27 years through 45 years who have not been adequately vaccinated, while acknowledging that benefit in this population may be limited because the vaccine is most effective if received before HPV exposure; however, assessing HPV vaccine status in patients with rheumatic disease, especially patients with SLE, should be done regularly.

Other Vaccines

There are many other vaccines to consider in patients with rheumatic diseases; hepatitis B and tetanus vaccinations are highlighted. Hepatitis B virus is transmitted through blood and sexual contact, and chronic hepatitis B infection increases risk for cirrhosis and liver cancer. ACIP recommendations for adult hepatitis B vaccination are risk based rather than universal (but universally recommended for newborns within 24 hours of birth), and vaccination is recommended for adults with certain risk factors, including chronic liver disease (including hepatitis C, cirrhosis, alcoholic liver disease, and autoimmune hepatitis), HIV, diabetes, intravenous drug use, men having sex with men, dialysis, and health care work[20] Anyone seeking protection from hepatitis B also may be vaccinated. Assessing hepatitis B risk is an opportune time to ensure that screening for chronic hepatitis B (and hepatitis C) has been done, because this is recommended (hepatitis B surface antigen, core, and surface antibodies) by the American Association for the Study of Liver Diseases prior to initiation of any immunosuppressive medication.[21]

Tetanus, diphtheria, and pertussis (Tdap) vaccination is recommended for anyone who previously did not receive Tdap at or after age 11, followed by a booster of

Tdap or tetanus and diphtheria vaccine every 10 years.[6] There are no special recommendations for immunocompromised persons regarding routine Tdap vaccination.

EFFECT OF IMMUNOSUPPRESSION ON VACCINE EFFICACY

Treatment with both conventional and biologic DMARDs can pose challenges to vaccine administration because their use can have an impact on vaccine responses. Impact on vaccine efficacy is dependent on type of immunosuppressive agent or combination of agents as well as timing of vaccine administration in relation to dosing, which is pertinent for biologics. When possible, immunizations should be administered prior to planned immunosuppression, and there are some therapies for which this is more important (eg, rituximab). Although the effect of newer biologic classes (inhibitors of JAK, interleukin [IL]-6 and IL-17 targeted therapies, and so forth) on vaccine efficacy are still being learned about, there is a growing amount of data demonstrating a negative impact of rituximab as well as methotrexate on response to influenza and pneumococcal vaccines.

Conventional Synthetic Disease-Modifying Antirheumatic Drugs

Methotrexate

Although there are data to suggest that serologic response to seasonal inactivated influenza vaccine in patients with rheumatic diseases appears to offer sufficient protection from influenza and its complications,[5] it is known that methotrexate impairs influenza vaccine responses.[22] Park and colleagues[23] examined the impact on immunogenicity of holding methotrexate for 2 doses after administration of inactivated quadrivalent influenza vaccine. In a prospective, randomized parallel-group multicenter study of 320 patients with RA, 75.5% in the methotrexate-hold group achieved a satisfactory vaccine response compared with 54.5% in the group that continued methotrexate, with higher seroprotection rates against all 4 antigens. There was a trend toward more disease flares in the methotrexate-hold group; however, it was not statistically significant. These findings are likely to be practice-changing, and holding methotrexate for 2 doses after seasonal influenza vaccination is a recommendation I make to my patients who have stable/inactive chronic inflammatory arthritis.

Methotrexate decreases humoral response to both the pneumococcal conjugate and polysaccharide vaccines.[24,25] Both the ACR and EULAR guidelines counsel that vaccines should preferably be administered prior to initiation of immunosuppression; however, this not always is possible. At present, there are no formal recommendations to hold methotrexate for the pneumococcal vaccine series.

Other disease-modifying antirheumatic drugs

Aside from methotrexate, there is little evidence to suggest a negative impact of other DMARDs, such as hydroxychloroquine, sulfasalazine, or leflunomide, on vaccine responses.[26,27] It is unlikely that azathioprine reduces vaccine efficacy; however, there have been conflicting reports of response to influenza vaccine, with a study in renal transplant patients showing no negative impact from azathioprine,[28] whereas a study in patients with SLE demonstrated a trend toward decreased vaccine efficacy, as evidenced by fewer seroconversions and appropriate rises in hemagglutinin inhibition titers compared with SLE patients receiving hydroxychloroquine, prednisone, or no drug.[29] Mycophenolate reduces influenza vaccine responses, seroprotection rates, and seroconversion rates in renal transplant patients, and in SLE patients its use has been associated with reduced response to HPV vaccine compared with use of other DMARDs.[26] At present, there are no recommendations to hold DMARD therapy for administration of any nonlive vaccine.

Biologics

Rituximab

Of all the biologics, rituximab has been shown to have the most significant impact on vaccine responses across different rheumatic disease and has the most profound impact on influenza and pneumococcal vaccine responses. This effect is further reduced by concomitant use of methotrexate. In a study examining antibody response to pneumococcal vaccine in 88 RA patients receiving rituximab, abatacept or tocilizumab with or without methotrexate, only 10.3% of patients receiving rituximab and no patients receiving rituximab with methotrexate achieved a positive antibody response.[30] It is recommended by both ACR and EULAR to time vaccine administration accordingly. Specifically, for a patient planning to start or already receiving rituximab, influenza and pneumococcal vaccines should be given at least 6 months after administration and 4 weeks before the next course of B-cell–depleting therapy, when possible.[2,31] If timing influenza vaccine administration prior to rituximab dosing to maximize efficacy is not feasible, some protection against influenza is better than none at all, and influenza vaccine should be given regardless, taking into account potential for suboptimal response.

Inhibitors of tumor necrosis factor

Aside from B-cell–depleting biologics, such as rituximab, other biologic DMARDs have various impacts on vaccine responses. Tumor necrosis factor (TNF) inhibitors have little to no effect on antibody response to the pneumococcal vaccine series or influenza vaccines. A systematic review of 12 studies assessing the impact of immunosuppressive therapies on humoral response to pneumococcal and influenza vaccines in RA patients found no association between TNF inhibition and reduced vaccine responses,[32] and this has been demonstrated in numerous other studies.[25] Although this is reassuring, TNF inhibitors often are used with methotrexate, so impact of methotrexate on vaccine response in this setting must be considered.

Abatacept

There is little consistent evidence to date suggesting a negative impact of abatacept, a T-cell costimulation modulator approved for treatment of RA, juvenile idiopathic arthritis, and psoriatic arthritis, on vaccine responses; however, there have been case reports suggesting blunted response. As with other biologics, most studies have examined the drug's impact on influenza and pneumococcal vaccines. In the study discussed previously, by Crnkic Kapetanovi, and colleagues,[30] abatacept-treated RA patients receiving pneumococcal conjugate vaccine did exhibit impaired antibody responses compared with controls but to a lesser degree than the group receiving rituximab. In an analysis of 2 multicenter open-label substudies of abatacept in RA, patients receiving weekly subcutaneous abatacept mounted appropriate responses to both pneumococcal and influenza vaccines.[33]

Interleukin-6 inhibitors

There currently are 2 FDA-approved IL-6 inhibitors indicated for treatment of RA (tocilizumab and sarilumab) as well as for giant cell arteritis, juvenile idiopathic arthritis, and cytokine release syndrome from chimeric antigen receptor-T-cell therapy (tocilizumab). The most safety data exist for tocilizumab, because it was approved first (2010, in the United States) and to date there are no data to suggest any adverse impact of tocilizumab on vaccine responses; however, concomitant use of methotrexate may have an impact on vaccine responses.[34]

Janus kinase inhibitors

A growing number of JAK inhibitors are newer additions to the armamentarium of treatment options for rheumatic diseases, and most of the existing data on their impact on vaccine responses are with the agent tofacitinib. In a placebo-controlled study examining the effects of tofacitinib on pneumococcal and influenza vaccine immunogenicity in a group of 200 RA patients, Winthrop and colleagues[35] found that fewer tofacitinib-treated patients developed satisfactory responses to the pneumococcal polysaccharide vaccine (45.1% vs 68.4%, respectively) and pneumococcal titers also were lower with tofacitinib (and even lower if concomitant methotrexate). They observed similar rates of satisfactory influenza vaccine responses; however, fewer tofacitinib-treated patients developed protective influenza titers although overall effect was felt to be minimal.

Other biologics

There are numerous other newer targeted therapies, including inhibitors of IL-17 and IL-12/23, and there is a paucity of evidence to suggest these agents have a negative impact on vaccine responses. Small studies have shown no impact on immunogenic response to seasonal influenza vaccine and PPSV23 in the setting of anti–IL-17 therapy for treatment of inflammatory arthritis (secukinumab)[36] or in healthy persons (ixekizumab).[37]

Immunosuppression and live vaccines

In general, administration of live vaccines (yellow fever, varicella, measles, and mumps rubella) is contraindicated in the setting of immunosuppressive therapy, as defined by the CDC (**Box 1**), as well as biologic DMARDs. There are circumstances under which rheumatic disease patients need a live vaccine (job requirements, school requirements, and so forth), and experts recommend that any live vaccine be give 4 weeks prior to immunosuppressive treatment initiation. For patients already on biologic therapy, there are no formal recommendations of how long to hold therapy if live vaccine is needed and this has not been heavily studied. Experts recommend holding immunosuppression at least 1 month before and 1 month after vaccination.

Of interest are safety data regarding the measles, mumps, and rubella (MMR) vaccine and LZV, suggesting there may be exceptions to the rule. Evidence for potential safety of MMR administration is drawn from the pediatric rheumatic disease population, where several studies have demonstrated appropriate vaccine responses as well as safety of MMR vaccine in juvenile idiopathic arthritis patients receiving methotrexate, etanercept, and other biologics.[38,39]

Box 1
Centers for Disease Control and Prevention–defined immunosuppressive therapy during which live vaccine administration should be avoided

- Methotrexate $\geq$0.4 mg/kg/wk
- Azathioprine $\geq$3 mg/kg/d
- 6-mercaptopurine $\geq$1.5 mg/kg/d
- Glucocorticoid usage $\geq$2 weeks in doses equivalent to prednisone 20 mg/d or 2 mg/kg body weight

Adapted from Centers for Disease Control and Prevention (CDC). Vaccine Recommendations and Guidelines of the ACIP. Available at: https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/contraindications.html. Accessed Sept 2 2020.

Administration of the LZV in the setting of tofacitinib has been studied, through a post hoc analysis of a phase IIB/IV randomized study of methotrexate-inadequate responders receiving tofacitinib, 5 mg twice daily; tofacitinib, 5 mg twice daily plus methotrexate; or adalimumab plus methotrexate to treat RA.[40] Of the 1146 patients, 216 (18.8%) received LZV 28 days before initiation of study treatment. Although the study was not powered for comparisons between vaccinated and nonvaccinated groups, the data suggest that LZV is well tolerated in tofacitinib-treated RA patients. The Varicella Zoster Vaccine study, a blinded 1:1 randomized placebo-controlled trial of LZV in patients receiving TNF inhibitors, identified no new safety concerns.[41] With the introduction of the more effective RZV to prevent HZ, safety concerns surrounding LZV administration in rheumatic disease patients is less of an issue, however, still pertinent in regions with limited or no access to RZV.

EFFECT OF VACCINES ON RHEUMATIC DISEASE ACTIVITY

Ideally, immunizations should be administered during quiescent disease, and this is supported by ACR and EULAR recommendations. Despite studies showing no evidence for an association between influenza vaccination and disease flare in patients with chronic inflammatory arthritis or SLE,[42] patients' concerns for side effects or disease flare remain barriers to vaccine uptake. There are some circumstances where this consideration becomes more pertinent, and these are discussed.

As discussed previously, RZV was not heavily studied in patients with autoimmune or inflammatory diseases, and the vaccine's increased risk of local and systemic injection site reactions has left many practitioners and patients hesitant to give/receive RZV to patients with rheumatic diseases. Although more studies on efficacy and safety in this patient population are needed, results of several small studies have been encouraging. In the largest study to date, Stevens and colleagues[15] retrospectively analyzed 403 rheumatic disease patients who received RZV at a single center and observed a disease flare incidence of 6.7% after vaccination and that of side effects (soreness at the injection site, rash, fever, stomach ache, nausea, and flulike symptoms) was 12.7%, both less than the incidence reported in the clinical trials that led to RZV approval. Although larger, prospective studies are needed to confirm these observations, these data provide a framework for shared and informed decision making between health care provider and patient. At present, I strongly recommend RZV in my rheumatic disease patient population, as long as their underlying disease is quiescent, and after discussing the potential adverse effects.

Also of note is a reported increased risk of gout, observed in the pivotal RZV trials,[13] which also has been observed in the setting of other vaccines and felt to be related to activation of the NLRP3 inflammasome by the adjuvant systems employed in various vaccines.[43] Although this is of interest, gout flare risk appears to be low, and avoiding vaccine administration due to concern for gout flare is not recommended. Along these same lines, pneumococcal vaccination has been associated with systemic adverse reaction in patients with autoinflammatory diseases, in particular cryopyrin-associated periodic syndromes, and should be administered with caution in this patient population.[44]

SUMMARY

Patients with rheumatic diseases have an increased risk of infection, and there are many vaccines available in the armamentarium to lower the risk of vaccine-preventable infections and their complications. Every effort should be made to routinely assess vaccine status and ensure that recommended vaccines are up to

date and administered prior to start of methotrexate and rituximab, when possible. Despite the known importance of routine vaccination in this vulnerable patient population, vaccine uptake remains low. Although there exist gaps in knowledge of vaccine efficacy in the setting of rheumatic diseases and immunosuppressive treatment, in particular, the newer biologics, and most of these recommendations are based on expert opinion/level C evidence, the information discussed in this article should provide a framework for rheumatologist and other health care providers to guide best practices and minimize infections in this at-risk population.

CLINICS CARE POINTS

- Seasonal flu vaccine should be actively recommended to all patients every year.
- The prime-boost pneumococcal vaccination method of administering PCV13 first followed by PPSV23 at least 8 weeks later should be given to all immunosuppressed rheumatic disease patients.
- Rituximab and methotrexate have the most significant impact on vaccine immunogenicity; influenza and pneumococcal vaccine administration should be timed prior to rituximab dosing and methotrexate held for 2 weeks after influenza vaccination when possible.
- The recombinant HZ vaccine has potential to cause injection site and systemic reactions, as well as rheumatic disease flare, but appears to be safe to administer and should be recommended, with informed decision making.

DISCLOSURE

C. Calabrese has consulted for AbBvie and consults and speaks for Sanofi-Regeneron.

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