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The effect of disease-modifying antirheumatic drugs on vaccine immunogenicity in adults

ABSTRACT

Patients with immunocompromising conditions are at higher risk of vaccine-preventable infections. Further, those receiving immunosuppressive disease-modifying antirheumatic drugs (DMARDs) can have variable responses to vaccines depending on which vaccine and which DMARD they are receiving.

KEY POINTS

Influenza vaccine should be given yearly to all patients on DMARDs, with modification to either the timing of DMARD or vaccine administration for patients receiving methotrexate or rituximab.

Pneumococcal vaccination should be given to all patients on DMARDs beginning at age 19 with pneumococcal 13-valent conjugate vaccine (PCV13) and then the 23-valent pneumococcal polysaccharide vaccine (PPSV23). Methotrexate, abatacept, tofacitinib, and rituximab reduce pneumococcal vaccine immunogenicity.

The live herpes zoster vaccine is contraindicated in those with severe immunosuppression (eg, those on biologics or Janus kinase inhibitors) but may be given to those on conventional synthetic DMARDs.

Limited data exist on the effects of DMARDs on human papillomavirus vaccine.

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PATIENTS CAN BECOME immunocompromised from primary or secondary causes. Primary causes are typically inherited, whereas secondary causes may be iatrogenic (ie, medication-related) or due to the underlying disease process. Infections represent a serious risk to patients who are immunocompromised, and the US Centers for Disease Control and Prevention (CDC) has developed specific vaccination recommendations for these individuals beginning at age 19.¹

Live vaccines are contraindicated in the severely immunocompromised, which, in patients receiving immunosuppressive drugs, is defined as those receiving any of the following:

- Prednisone in a dosage of 2 mg/kg or more, or more than 20 mg/day
- Methotrexate in a dosage of more than 0.4 mg/kg/week
- Azathioprine more than 3 mg/kg/day
- 6-Mercaptopurine more than 1.5 mg/kg/day
- Any biologic agent.²

In this review, we discuss the use of various vaccines in immunocompromised patients, with a focus on iatrogenic immunosuppression for patients with systemic rheumatic or other immune-mediated inflammatory diseases.

■ IMMUNE-MEDIATED INFLAMMATORY DISEASES AND INFECTION

Patients with immune-mediated inflammatory diseases such as rheumatoid arthritis, psoriatic arthritis, and Crohn disease are at increased risk of infections, often due to the immunosuppressive medications they need (Table 1).

TABLE 1

Selected disease-modifying antirheumatic drugs

Antimetabolite

Methotrexate

Tumor necrosis factor inhibitors

Adalimumab

Certolizumab

Etanercept

Golimumab

Infliximab

Anti-CD80/CD86

Abatacept

Janus kinase inhibitors

Baricitinib

Tofacitinib

Upadacitinib

Anti-CD20

Rituximab

Interleukin (IL-) 6 inhibitors

Sarilumab

Siltuximab

Tocilizumab

IL-17 inhibitors

Brodalumab

Ixekizumab

Secukinumab

IL-12/23 inhibitors

Ustekinumab

Vaccines should be offered when appropriate to reduce risk

A large, retrospective US study³ evaluated the incidence of hospitalization for infections in patients with rheumatoid arthritis who had no exposure to a biologic agent in the year preceding the study compared with those who switched among various biologic agents in the year preceding the study. The mean rate of hospitalization for infections was 4.6 per 100 person-years in biologic-naïve patients, compared with 7.0 for biologic-experienced patients switching to a new therapy. This suggests that those with more refractory disease (using switching of biologic drugs as a proxy for more treatment-refractory disease) were at greater risk of infection. Pneumonia and soft-tissue infections were the most common types of infections.

Risk stratification for patients at high risk is important in both counseling patients and

addressing modifiable risk factors for infection (eg, vaccination, tobacco use, glucocorticoid use). Infection risk calculators, such as the Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT) Risk Score,⁴ or similar approaches developed for use in large administrative databases,⁵ have been developed to estimate the yearly probability of a serious infection. The risk of most if not all types of infections is increased in patients with immune-mediated inflammatory diseases, and certain therapies for these disease further increase the risk. For example, the incidence of herpes zoster is higher in immune-mediated inflammatory diseases than in the general population and is further increased with Janus kinase inhibitors.⁶

More broadly, a systematic literature review of articles published from October 2009 to August 2018 was performed to determine the incidence and prevalence of vaccine-preventable illnesses in patients with autoimmune inflammatory rheumatic diseases.⁷ Of the 3,876 articles initially retrieved, 63 met the inclusion criteria that allowed for analysis of incidence and prevalence rates of influenza, pneumococcal disease, hepatitis B, herpes zoster, and human papillomavirus (HPV) infection. The rates of influenza, *Pneumococcus*, herpes zoster, and HPV infections were higher than those in the general population.

Due to the significant risk of infection in patients with autoimmune inflammatory rheumatic diseases, vaccines should be offered when appropriate to reduce the risk.^{1,8}

INFLUENZA VACCINATION

All adults, regardless of immunocompromised status, should receive a single dose of the annual influenza vaccine each year. Immunocompromised patients should receive either the recombinant influenza vaccine or the inactivated influenza vaccine¹; the live attenuated influenza vaccine is contraindicated in this population. An egg allergy is not an absolute contraindication, as cell-culture based vaccines are available.⁹

Which influenza vaccine to use?

The standard inactivated influenza vaccine is trivalent, containing 2 influenza A strains and 1 influenza B strain. A quadrivalent vaccine,

TABLE 2

Impact of disease-modifying antirheumatic drugs on vaccine immunogenicity

DMARDs	Influenza vaccine	PPSV23	PCV7/13	Live zoster vaccine	Recombinant zoster vaccine	Hepatitis B vaccine	Human papilloma-virus vaccine
Methotrexate	Decrease ^{14,15}	Decrease ^{14,24}	Decrease ²⁸	No effect ^{17,34}	Not studied	Not studied	No effect ^{40,41}
TNF inhibitors	No effect ¹⁴	No effect ^{14,24}	No effect ^{28,29}	Study pending, contraindicated ³⁵	Study pending	Decrease ^{37–39}	No effect ^{40,41}
Abatacept	No effect ¹⁶	No effect ¹⁶	Decrease ³⁰	Study pending, contraindicated	Study pending	Not studied	Not studied
Janus kinase inhibitors	No effect ¹⁷	Decrease ¹⁷	No effect ^{31,32}	Not studied, contraindicated	Study pending	Not studied	Not studied
Rituximab	Decrease ^{14,18,19}	Decrease ^{19,25}	Decrease ^{30,33}	Not studied, contraindicated	No effect ³⁶	Not studied	Not studied
IL-6 inhibitors	No effect ²⁰	No effect ²⁰	No effect ³⁰	Not studied, contraindicated	Not studied	Not studied	Not studied
IL-17 inhibitors	No effect ^{21–23}	No effect ²⁶	Not studied	Not studied, contraindicated	Not studied	Not studied	Not studied
IL-12/23 inhibitors	Not studied	No effect ²⁷	Not studied	Not studied, contraindicated	Not studied	Decrease ³⁸	Not studied

DMARDs = disease-modifying antirheumatic drugs; IL = interleukin; PCV7/13 = 7- or 13-valent pneumococcal conjugate vaccine; PPSV23 = 23-valent pneumococcal polysaccharide vaccine; TNF = tumor necrosis factor

also available, contains the standard strains with an additional influenza B (Yamagata) strain. A high-dose trivalent vaccine can be considered in individuals over age 65, as it confers a higher percentage of protective titers than the standard-dose vaccine and has been shown to have greater clinical effectiveness in preventing influenza infection.¹⁰

The recommendation to use the high-dose vaccine in at-risk individuals was further supported by a 2019 trial from Hong Kong that enrolled community-dwelling adults ages 65 to 82.¹¹ Sera were collected before and after vaccination with the 2017–2018 standard-dose quadrivalent, the trivalent with MF59 adjuvant, the high-dose trivalent, or the recombinant hemagglutinin quadrivalent vaccine. The MF59-adjuvanted trivalent, high-dose trivalent, and recombinant-hemagglutinin quadrivalent vaccines are considered enhanced vaccines, as either the increased dosage or use of an adjuvant causes a more

robust immunogenic response. The mean rise in titer to egg-propagated H1N1 and H3N2 and microneutralized H3N2 was significantly higher in all enhanced-vaccine groups than in the group that received the standard-dose quadrivalent vaccine.

Enhanced vaccination in patients with immune-mediated inflammatory diseases was evaluated in a randomized controlled trial in patients with rheumatoid arthritis.¹² The high-dose trivalent vaccine was compared with the standard-dose quadrivalent vaccine in 279 seropositive patients on conventional synthetic disease-modifying antirheumatic drugs (DMARDs), biologic DMARDs (tumor necrosis factor [TNF] inhibitors, anti-interleukin-6 [anti-IL-6]), or Janus kinase inhibitors. Even though this group of individuals was not selected for being age 65 or older (the mean age was 61.0 ± 12.9 years), the high-dose trivalent vaccine significantly improved immunogenicity compared with the standard-

dose vaccine. While clinical outcomes (eg, incidence of influenza infection) were not assessed, this laboratory finding likely indicates that high-dose vaccination is preferable for all rheumatoid arthritis patients, irrespective of age.

The choice of influenza vaccine may also depend on local virulence patterns, as the Yamagata strain, which is not covered by the high-dose trivalent vaccine, may be the primary strain, or at least a relatively common strain. Although not as common on a national scale in recent years, the Yamagata strain varies in prevalence from year to year and has accounted for a significant portion of influenza B in the recent past. A high-dose quadrivalent influenza vaccine that includes coverage for the Yamagata strain will be available for the 2020–2021 influenza season.¹³

Effect of DMARDs on influenza vaccine effectiveness

Most DMARDs do not have a major effect on influenza vaccine seroprotection (Table 2).^{14–41} However, rituximab significantly reduces it.^{14,18,19} Rituximab is typically given every 6 months, and vaccination should be given about 2 weeks before the next rituximab dose.¹⁸

Methotrexate also decreases seroprotection from the influenza vaccine, but to a lesser degree than rituximab.^{14,15} Holding methotrexate dosing for 2 weeks after influenza vaccination can improve vaccine seroprotection, as was demonstrated in a randomized controlled trial conducted among rheumatoid arthritis patients in Korea.¹⁵ The diminution of beneficial effect of vaccination was related to methotrexate dose, and patients receiving 15 mg or more per week had a more reduced response than those on lower methotrexate doses. Patients on even lower but commonly used methotrexate doses had a minimal effect of methotrexate on vaccine immunogenicity.

TNF inhibitors,¹⁴ abatacept,¹⁶ tofacitinib,¹⁷ tocilizumab,²⁰ and secukinumab^{21–23} have not been shown to substantially reduce the proportion of patients who achieve adequate seroprotection.

While most studies have evaluated only the laboratory outcome of immunogenicity as a surrogate for clinical effectiveness, some

observational studies have examined clinical outcomes such as the incidence of infection.⁴² A retrospective observational study⁴² of 30,788 patients with immune-mediated inflammatory diseases compared those who received and did not receive vaccination. In propensity score-adjusted analysis, vaccination reduced the risks of:

- Influenza-like illness (adjusted hazard ratio [aHR] 0.70, 95% confidence interval [CI] 0.54–0.92)
- Hospitalization for pneumonia (aHR 0.61, 95% CI 0.50–0.75)
- Hospitalization for chronic obstructive pulmonary disease exacerbation (aHR 0.67, 95% CI 0.46–0.99)
- Death due to pneumonia (aHR 0.48, 95% CI 0.33–0.71).

PNEUMOCOCCAL VACCINATION

For immunocompromised patients such as those with immune-mediated inflammatory diseases, pneumococcal vaccination is recommended starting at age 19.¹ Immunocompromised individuals should first receive a single dose of PCV13. A dose of PPSV23 follows, at least 8 weeks later. A second dose of PPSV23 is recommended 5 years after the first dose of PPSV23. After a second dose of PPSV23, no further booster vaccinations are recommended. Additionally, individuals who received PPSV23 before age 65 for any indication should receive another dose at least 5 years later. For those who received PPSV23 before PCV13, PCV13 should be given at least 1 year after PPSV23.

Effect of DMARDs on pneumococcal vaccine effectiveness

Similar to influenza vaccination, most DMARDs have limited effects on pneumococcal vaccine immunogenicity (Table 2). Methotrexate and rituximab, however, decrease the humoral response to pneumococcal vaccine.^{14,19,24,25,28–30,33,36}

A systematic review and meta-analysis was performed to determine the effects of methotrexate, TNF inhibitors, and rituximab on the immunogenicity of the influenza and pneumococcal vaccines in patients with rheumatoid arthritis.¹⁴ Twelve studies were included in the analysis, but only 2 of them specifically

A high-dose quadrivalent flu vaccine that covers the Yamagata strain will be available for the 2020–2021 season

tested methotrexate's effect on pneumococcal vaccine effectiveness.^{24,28} Methotrexate significantly reduced the vaccine response against pneumococcal serotypes 6B and 23F, with a pooled odds ratio (OR) of 0.33 (95% CI 0.20–0.54) for 6B and 0.58 (0.36–0.94) for 23F. These serotypes were chosen because they were commonly seen in invasive pneumococcal disease both worldwide and in Sweden, where the study was performed.

Similarly, only 2 of the studies evaluated the effect of rituximab.^{19,33} Serotype 6B immunogenicity was significantly reduced with rituximab (OR 0.25, 95% CI 0.11–0.58), and there was a trend toward a similar reduction for serotype 23F (OR 0.21, 95% CI 0.04–1.05). Later studies have also shown a significant reduction in both 6B and 23F serotype immunogenicity with rituximab compared with controls.³⁰ The addition of methotrexate to rituximab further reduced immunogenicity.

Similar to the recommendation for the timing of influenza vaccination in patients treated with rituximab, pneumococcal vaccination should be given as close to the start of a subsequent rituximab dosing cycle as possible (eg, approximately 2 weeks before the next rituximab cycle).

Tofacitinib also decreases the humoral response to PPSV23,¹⁷ yet both tofacitinib and baricitinib showed that a high percentage of patients who received PCV13 while on these treatments were able to mount a satisfactory immune response, although there was no control group in those studies.^{31,32} TNF inhibitors have not been shown to have a significant effect on humoral response in PPSV23^{14,24} or PCV7²⁸ in the absence of concomitant methotrexate. Tocilizumab did not reduce response to PPSV23²⁰ or PCV7.³⁰ Ixekizumab²⁶ and ustekinumab²⁷ did not significantly reduce immunogenicity to PPSV23 in healthy controls or in patients with moderate-to-severe psoriasis respectively, but PCV13 has not been studied for patients receiving these classes of biologics.

■ HERPES ZOSTER VACCINATION

Herpes zoster vaccination in the general population is recommended starting at age 50 with a 2-dose series of recombinant zoster vaccine.¹

Many primary care practices have stopped using the live zoster vaccine (Zostavax), as recombinant zoster vaccine (Shingrix) is more effective,⁴³ and the live zoster vaccine was discontinued in the United States in July 2020.⁴⁴

The guideline published by the American College of Rheumatology in 2015 recommended live zoster vaccination for all patients with rheumatoid arthritis who are at least age 50.⁸ Recommendations to use recombinant zoster vaccine among rheumatology patients have not yet been formulated or issued, and we currently have few data on its efficacy, safety (eg, risk of disease flare), and systemic reactogenicity in these populations.

Recombinant zoster vaccine is not a live vaccine. However, its clinical trials excluded people who were considered severely immunocompromised and also those with rheumatoid arthritis, systemic lupus erythematosus, and similar diseases receiving typical immunomodulatory therapies (eg, conventional synthetic DMARDs, biologics, and Janus kinase inhibitors). There is at least the potential concern for flare of underlying autoimmune conditions with recombinant zoster vaccine due to the potent immune response stimulated by the adjuvant.⁴⁵ Recombinant zoster vaccine is currently being studied in patients with immune-mediated inflammatory diseases and a variety of other immunocompromised patient populations.¹

Although recombinant zoster vaccine is not yet recommended for patients with immune-mediated inflammatory diseases, a retrospective review of 300 patients with rheumatic disease who received it showed only a 3% incidence of rheumatoid arthritis flare within 12 weeks of vaccination and no cases of herpes zoster reactivation.⁴⁶ Key limitations of this study included retrospective flare ascertainment, as recorded by documentation in rheumatologists' medical records, rather than prospective and systematic capture of flare and severe reactogenicity according to validated prespecified case definitions.

Despite US recommendations that favor recombinant over live zoster vaccine for healthy older patients, there are a number of countries worldwide in which it is not available, and the live vaccine remains the only option for herpes zoster vaccination. How-

Methotrexate and rituximab decrease the humoral response to pneumococcal vaccine

ever, since it is a live vaccine, there are potential concerns about transmitting infection to patients with severe immunosuppression. The CDC⁴⁷ says its use is acceptable for patients treated with:

- Methotrexate ≤ 0.4 mg/kg/week
- Azathioprine ≤ 3.0 mg/kg/day
- 6-Mercaptopurine ≤ 1.5 mg/kg/day
- Prednisone < 20 mg/day or equivalent
- Intra-articular, intrabursal, or peritendinous corticosteroid injections.

For patients with rheumatoid arthritis who are at least 50 years old, the live zoster vaccine, if used, should be given before starting DMARDs or biologics whenever possible,⁸ as incidence rates of herpes zoster have been shown to be increased and occur at an earlier age in patients with rheumatic and inflammatory diseases when compared to healthy individuals.⁶ For example, the risk of herpes zoster in rheumatoid arthritis patients in their 40s is approximately equal to or higher than that in healthy older persons in their 60s.

Use of live zoster vaccine has also been shown to be safe and immunogenic when given 2 to 3 weeks before starting tofacitinib in patients with rheumatoid arthritis, but its long-term efficacy was unclear and did not seem to lower the risk of herpes zoster in follow-up of this small cohort.³⁴

Due to the disease burden of herpes zoster in this population and uncertainties regarding the safety of live zoster vaccine in patients receiving biologic therapies, a randomized, blinded, placebo-controlled trial of live zoster vaccine in patients age 50 and older treated with TNF inhibitors for any on-label or off-label indication was performed to evaluate for safety and immunogenicity.³⁵ The study randomized 617 participants, and there were no cases of disseminated or local varicella infection in the 6-week period following live zoster vaccination, the at-risk period of concern. The immunologic effectiveness of live zoster vaccine in this trial is still being evaluated.

HEPATITIS B VACCINATION

In those who were not vaccinated as children, hepatitis B vaccination is not recommended routinely in the United States for adult rheumatic disease patients, but only in those for

whom special situations or circumstances increase the risk for transmission.¹ These circumstances include:

- Hepatitis C virus co-infection
- Other chronic liver disease
- Human immunodeficiency virus infection
- High-risk sexual behavior
- Injection drug use
- Other high risk for percutaneous or mucosal exposure
- Incarceration
- Travel to countries with high or intermediate endemic hepatitis B.

Practitioners other than rheumatologists may give different recommendations for hepatitis B vaccination. For example, gastroenterologists routinely recommend it for patients with inflammatory bowel disease regardless of age.⁴⁸

Three hepatitis B vaccines are currently available:

- Heplisav-B, given in a 2-dose series
- Engerix-B or Recombivax HB, given in a 3-dose series
- Twinrix, a combination hepatitis A and B vaccine given in a 3-dose series.

Effect of DMARDs on hepatitis B vaccine effectiveness

The effect of most DMARDs on hepatitis B vaccine immunogenicity has not been evaluated (Table 2); however, TNF inhibitors and ustekinumab have been shown to reduce it.^{37,38,39} Response to the hepatitis B vaccine depends on T-cell activation, and the impairment of T-cell response caused by TNF inhibitors and ustekinumab (and presumably other IL-12/23 inhibitors) is thought to lead to the diminished response.⁴⁹ Several strategies may be needed to improve the immune response to hepatitis B vaccine, including repeated vaccine series, intradermal vaccine administration, development of new vaccine adjuvants, and high-dose vaccines.

A high-dose vaccine containing 40 μ g/mL (the usual dose is 20 μ g/mL) was studied in 109 patients with various rheumatologic and inflammatory diseases who were treated with TNF inhibitors or ustekinumab.³⁸ The development of a protective antibody titer was seen in 49.3% of patients who received the standard-dose vaccine and in 61.1% of those given

Recombinant zoster vaccine is more effective than the live vaccine, but new recommendations for rheumatology patients are yet to be issued

the high-dose vaccine. The difference was not statistically significant, however ($P = .246$).

Given the likelihood of nonresponse in these groups, it is important that the clinician evaluate for response with postvaccine hepatitis B surface antibody titers to determine if protection has been achieved, with adequate seroprotection typically defined as a titer of 10 mIU/mL or higher.⁵⁰

■ HUMAN PAPILLOMAVIRUS VACCINATION

Vaccination against HPV is recommended for all adults through age 26, with initial vaccination routinely recommended in adolescents at age 11 or 12.^{1,51} Using shared decision-making, HPV vaccination may also be offered to those ages 27 to 45. The age of initial HPV vaccination determines the number of vaccinations given in the series, with a total of 2 or 3 doses comprising a complete series.

Although 3 HPV vaccines are licensed for use, only the 9-valent HPV vaccine (Gardasil 9) is available in the United States; it covers HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58. Most HPV-associated cancers are caused by HPV types 16 or 18. There is no recommendation to alter the vaccination schedule for HPV in immunocompromised conditions.

Women with immune-mediated inflammatory diseases and those receiving immunosuppressive medications are at higher risk of HPV infection leading to high-grade cervical dysplasia and cervical cancer. However, vaccination rates are low.^{7,52} Given these concerns, it is important to be aware of barriers to care. Many patients with immune-mediated inflammatory diseases receive vaccinations from their rheumatologists, who may not routinely stock the HPV vaccine. Further, given the complexity of many immune-mediated inflammatory diseases, discussions about preventive care may be deferred. Efforts should be made by both rheumatologists and those in the primary care specialties to encourage vaccination.

Effects of DMARDs on HPV vaccine effectiveness

Few studies have examined the effects of DMARDs on the immunogenicity of the

HPV vaccine (Table 2). A 2013 prospective, controlled observational study compared the immunogenicity of a bivalent HPV vaccine in 68 girls with juvenile idiopathic arthritis compared with 55 healthy girls.⁴⁰ Use of methotrexate did not affect seroconversion. In addition, the rates of seroconversion were not significantly lower in the patients receiving TNF inhibitors; however, the number of patients was considered to be too low to draw strong conclusions.

The effect of TNF inhibitors on HPV vaccine effectiveness was also evaluated in a prospective cohort of 37 female patients ages 9 to 26 with inflammatory bowel disease compared with matched healthy controls from a database.⁴¹ Patients treated with the TNF inhibitors adalimumab or infliximab comprised 51% of the cohort, and the remaining 49% were on other immunomodulators including azathioprine, 6-mercaptopurine, methotrexate, cyclosporine, and tacrolimus. Overall, there was no difference in rates of seropositivity between the inflammatory bowel disease patients and the healthy controls.

There are currently no studies evaluating the effects of abatacept, Janus kinase inhibitors, rituximab, anti-IL-6, anti-IL-17, or anti-IL-12/23 inhibitors on the immunogenicity of the HPV vaccine.

■ TAKE-HOME POINTS

- Immunocompromised patients are at increased risk of infection due to their primary condition or secondarily due to treatment.
- Vaccination provides an important method of prevention, but use of live vaccines is not recommended in severely immunocompromised persons.
- Non-live vaccines can be used at any time, although preferably they should be given before use of DMARDs in order to minimize negative effects on immunogenicity where they exist.
- For current DMARD users, temporarily holding methotrexate for influenza vaccination could be considered, and most importantly for rituximab, vaccination should occur near the end of the treatment interval 1 month before the next planned dose.

TNF inhibitors and ustekinumab reduce hepatitis B vaccine immunogenicity

REFERENCES

1. Freedman M, Kroger A, Hunter P, Ault KA; Advisory Committee on Immunization Practices. Recommended adult immunization schedule, United States, 2020. *Ann Intern Med* 2020; 172(5):337–347. doi:10.7326/M20-0046
2. Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clin Infect Dis* 2014; 58(3):e44–e100. doi:10.1093/cid/cit684
3. Curtis JR, Xie F, Chen L, et al. The comparative risk of serious infections among rheumatoid arthritis patients starting or switching biological agents. *Ann Rheum Dis* 2011; 70(8):1401–1406. doi:10.1136/ard.2010.146365
4. Zink A, Manger B, Kaufmann J, et al. Evaluation of the RABBIT Risk Score for serious infections. *Ann Rheum Dis* 2014; 73(9):1673–1676. doi:10.1136/annrheumdis-2013-203341
5. Curtis JR, Xie F, Chen L, et al. Use of a disease risk score to compare serious infections associated with anti-tumor necrosis factor therapy among high- versus lower-risk rheumatoid arthritis patients. *Arthritis Care Res (Hoboken)* 2012; 64(10):1480–1489. doi:10.1002/acr.21805
6. Yun H, Yang S, Chen L, et al. Risk of herpes zoster in autoimmune and inflammatory diseases: implications for vaccination. *Arthritis Rheumatol* 2016; 68(9):2328–2337. doi:10.1002/art.39670
7. Furer V, Rondaan C, Heijstek M, et al. Incidence and prevalence of vaccine preventable infections in adult patients with autoimmune inflammatory rheumatic diseases (AIIRD): a systemic literature review informing the 2019 update of the EULAR recommendations for vaccination in adult patients with AIIRD. *RMD Open* 2019; 5(2):e001041. doi:10.1136/rmdopen-2019-001041
8. Singh JA, Saag KG, Bridges SL Jr, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol* 2016; 68(1):1–26. doi:10.1002/art.39480
9. Cox MM, Patriarca PA, Treanor J. FluBlok, a recombinant hemagglutinin influenza vaccine. *Influenza Other Respir Viruses* 2008; 2(6):211–219. doi:10.1111/j.1750-2659.2008.00053.x
10. DiazGranados CA, Dunning AJ, Kimmel M, et al. Efficacy of high-dose versus standard-dose influenza vaccine in older adults. *N Engl J Med* 2014; 371(7):635–645. doi:10.1056/NEJMoa1315727
11. Cowling BJ, Perera RAPM, Valkenburg SA, et al. Comparative Immunogenicity of several enhanced influenza vaccine options for older adults: a randomized, controlled trial. *Clin Infect Dis* 2019; ciz1034. doi:10.1093/cid/ciz1034
12. Colmegna I, Useche M, Rodriguez K, et al. Efficacy of high-dose versus standard-dose influenza vaccine in seropositive rheumatoid arthritis patients. *Arthritis Rheumatol* 2018; 70(suppl 10).
13. Sanofi Pasteur Inc. Package Insert: Fluzone high-dose quadrivalent. <https://www.fda.gov/media/132238/download>. Accessed October 12, 2020.
14. Hua C, Barnette T, Combe B, Morel J. Effect of methotrexate, anti-tumor necrosis factor α , and rituximab on the immune response to influenza and pneumococcal vaccines in patients with rheumatoid arthritis: a systematic review and meta-analysis. *Arthritis Care Res (Hoboken)* 2014; 66(7):1016–1026. doi:10.1002/acr.22246
15. Park JK, Lee MA, Lee EY, et al. Effect of methotrexate discontinuation on efficacy of seasonal influenza vaccination in patients with rheumatoid arthritis: a randomised clinical trial. *Ann Rheum Dis* 2017; 76(9):1559–1565. doi:10.1136/annrheumdis-2017-211128
16. Alten R, Bingham CO 3rd, Cohen SB, et al. Antibody response to pneumococcal and influenza vaccination in patients with rheumatoid arthritis receiving abatacept. *BMC Musculoskelet Disord* 2016; 17:231. doi:10.1186/s12891-016-1082-z
17. Winthrop KL, Silverfield J, Racewicz A, et al. The effect of tofacitinib on pneumococcal and influenza vaccine responses in rheumatoid arthritis. *Ann Rheum Dis* 2016; 75(4):687–695. doi:10.1136/annrheumdis-2014-207191
18. van Assen S, Holvast A, Benne CA, et al. Humoral responses after influenza vaccination are severely reduced in patients with rheumatoid arthritis treated with rituximab. *Arthritis Rheum* 2010; 62(1):75–81. doi:10.1002/art.25033
19. Bingham CO 3rd, Looney RJ, Deodhar A, et al. Immunization responses in rheumatoid arthritis patients treated with rituximab: results from a controlled clinical trial. *Arthritis Rheum* 2010; 62(1):64–74. doi:10.1002/art.25034
20. Tsuru T, Terao K, Murakami M, et al. Immune response to influenza vaccine and pneumococcal polysaccharide vaccine under IL-6 signal inhibition therapy with tocilizumab. *Mod Rheumatol* 2014; 24(3):511–516. doi:10.3109/14397595.2013.843743
21. Furer V, Zisman D, Kaufman I, et al. Immunogenicity and safety of vaccination against seasonal influenza vaccine in patients with psoriatic arthritis treated with secukinumab. *Vaccine* 2020; 38(4):847–851. doi:10.1016/j.vaccine.2019.10.081
22. Chioato A, Noseda E, Stevens M, Gaitatzis N, Kleinschmidt A, Picard H. Treatment with the interleukin-17A-blocking antibody secukinumab does not interfere with the efficacy of influenza and meningococcal vaccinations in healthy subjects: results of an open-label, parallel-group, randomized single-center study. *Clin Vaccine Immunol* 2012; 19(10):1597–1602. doi:10.1128/CVI.00386-12
23. Richi P, Martín MD, de Ory F, et al. Secukinumab does not impair the immunogenic response to the influenza vaccine in patients. *RMD Open* 2019; 5(2):e001018. doi:10.1136/rmdopen-2019-001018
24. Kapetanovic MC, Saxne T, Sjöholm A, Truedsson L, Jönsson G, Geborek P. Influence of methotrexate, TNF blockers and prednisolone on antibody responses to pneumococcal polysaccharide vaccine in patients with rheumatoid arthritis. *Rheumatology (Oxford)* 2006; 45(1):106–111. doi:10.1093/rheumatology/kei193
25. Nazi I, Kelton JG, Larché M, et al. The effect of rituximab on vaccine responses in patients with immune thrombocytopenia. *Blood* 2013; 122(11):1946–1953. doi:10.1182/blood-2013-04-494096
26. Gomez EV, Bishop JL, Jackson K, Muram TM, Phillips D. Response to tetanus and pneumococcal vaccination following administration of ixekizumab in healthy participants. *BioDrugs* 2017; 31(6):545–554. doi:10.1007/s40259-017-0249-y
27. Brodmerkel C, Wadman E, Langley RG, et al. Immune response to pneumococcus and tetanus toxoid in patients with moderate-to-severe psoriasis following long-term ustekinumab use. *J Drugs Dermatol* 2013; 12(10):1122–1129. pmid:24085047
28. Kapetanovic MC, Roseman C, Jönsson G, Truedsson L, Saxne T, Geborek P. Antibody response is reduced following vaccination with 7-valent conjugate pneumococcal vaccine in adult methotrexate-treated patients with established arthritis, but not those treated with tumor necrosis factor inhibitors. *Arthritis Rheum* 2011; 63(12):3723–3732. doi:10.1002/art.30580
29. Farmaki E, Kanakoudi-Tsakalidou F, Spoulou V, et al. The effect of anti-TNF treatment on the immunogenicity and safety of the 7-valent conjugate pneumococcal vaccine in children with juvenile idiopathic arthritis. *Vaccine* 2010;

HPV vaccine is effective, but vaccination rates are low

- 28(31):5109–5113. doi:10.1016/j.vaccine.2010.03.080
30. **Crnkic Kapetanovic M, Saxne T, Jönsson G, Truedsson L, Geborek P.** Rituximab and abatacept but not tocilizumab impair antibody response to pneumococcal conjugate vaccine in patients with rheumatoid arthritis. *Arthritis Res Ther* 2013; 15(5):R171. doi:10.1186/ar4358
 31. **Winthrop KL, Bingham CO 3rd, Komocsar WJ, et al.** Evaluation of pneumococcal and tetanus vaccine responses in patients with rheumatoid arthritis receiving baricitinib: results from a long-term extension trial substudy. *Arthritis Res Ther* 2019; 21(1):102. doi:10.1186/s13075-019-1883-1
 32. **Winthrop KL, Korman N, Abramovits W, et al.** T-cell-mediated immune response to pneumococcal conjugate vaccine (PCV-13) and tetanus toxoid vaccine in patients with moderate-to-severe psoriasis during tofacitinib treatment. *J Am Acad Dermatol* 2018; 78(6):1149–1155. e1. doi:10.1016/j.jaad.2017.09.076
 33. **Kapetanovic MC, Roseman C, Jonsson G, Truedsson L, Saxne T, Geborek P.** Rituximab and methotrexate but not TNF-blockers are associated with impaired antibody response following pneumococcal vaccination using 7-valent conjugate vaccine (Prevenar) in patients with established rheumatoid arthritis. *Arthritis Rheum* 2011. <https://acr.confex.com/acr/2011/webprogram/Paper19167.html>. Accessed October 12, 2020.
 34. **Winthrop KL, Wouters AG, Choy EH, et al.** The safety and immunogenicity of live zoster vaccination in patients with rheumatoid arthritis before starting tofacitinib: a randomized phase ii trial. *Arthritis Rheumatol* 2017; 69(10):1969–1977. doi:10.1002/art.40187
 35. **Curtis J, Bridges S, Cofield S, et al.** Results from a randomized controlled trial of the safety of the live varicella vaccine in TNF-treated patients. *Arthritis Rheumatol* 2019; 71 (suppl 10). Accessed October 12, 2020.
 36. **Parrino J, McNeil SA, Lawrence SJ, et al.** Safety and immunogenicity of inactivated varicella-zoster virus vaccine in adults with hematologic malignancies receiving treatment with anti-CD20 monoclonal antibodies. *Vaccine* 2017; 35(14):1764–1769. doi:10.1016/j.vaccine.2016.10.055
 37. **Gisbert JP, Villagrasa JR, Rodríguez-Nogueiras A, Chaparro M.** Efficacy of hepatitis B vaccination and revaccination and factors impacting on response in patients with inflammatory bowel disease. *Am J Gastroenterol* 2012; 107(10):1460–1466. doi:10.1038/ajg.2012.79
 38. **Haykir Solay A, Eser F.** High dose hepatitis B vaccine is not effective in patients using immunomodulatory drugs: a pilot study. *Hum Vaccin Immunother* 2019; 15(5):1177–1182. doi:10.1080/21645515.2019.1574151
 39. **Salinas GF, De Rycke L, Barendregt B, et al.** Anti-TNF treatment blocks the induction of T cell-dependent humoral responses. *Ann Rheum Dis* 2013; 72(6):1037–1043. doi:10.1136/annrheumdis-2011-201270
 40. **Heijstek MW, Scherpenisse M, Groot N, et al.** Immunogenicity and safety of the bivalent HPV vaccine in female patients with juvenile idiopathic arthritis: a prospective controlled observational cohort study. *Ann Rheum Dis* 2014; 73(8):1500–1507. doi:10.1136/annrheumdis-2013-203429
 41. **Jacobson DL, Bousvaros A, Ashworth L, et al.** Immunogenicity and tolerability to human papillomavirus-like particle vaccine in girls and young women with inflammatory bowel disease. *Inflamm Bowel Dis* 2013; 19(7):1441–1449. doi:10.1097/MIB.0b013e318281341b
 42. **Nakafero G, Grainge MJ, Myles PR, et al.** Effectiveness of inactivated influenza vaccine in autoimmune rheumatic diseases treated with disease-modifying anti-rheumatic drugs. *Rheumatology (Oxford)* 2020. [Epub ahead of print] doi:10.1093/rheumatology/keaa078
 43. **Dooling KL, Guo A, Patel M, et al.** Recommendations of the Advisory Committee on Immunization Practices for Use of Herpes Zoster Vaccines. *MMWR Morb Mortal Wkly Rep* 2018; 67(3):103–108. doi:10.15585/mmwr.mm6703a5
 44. **MerckVaccines.** Supply status. <https://ordering.merckvaccines.com/supply-status>. Accessed October 12, 2020.
 45. **Lal H, Cunningham AL, Godeaux O, et al.** Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. *N Engl J Med* 2015; 372(22):2087–2096. doi:10.1056/NEJMoa1501184
 46. **Stevens E, Weinblatt ME, Massarotti E, Griffin F, Desai S.** FRI0068 Safety of the zoster recombinant adjuvanted vaccine in rheumatoid arthritis patients: a single center's experience with 300 patients. *Ann Rheum Dis* 2019; 78(suppl 2):695.
 47. **Centers for Disease Control and Prevention.** Vaccine recommendation and guidelines of the ACIP. Contraindications and precautions. <https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/contraindications.html>. Accessed October 12, 2020.
 48. **Terrault NA, Lok ASF, McMahon BJ, et al.** Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology* 2018; 67(4):1560–1599. doi:10.1002/hep.29800
 49. **Saco TV, Strauss AT, Ledford DK.** Hepatitis B vaccine nonresponders: possible mechanisms and solutions. *Ann Allergy Asthma Immunol* 2018; 121(3):320–327. doi:10.1016/j.anai.2018.03.017
 50. **Schillie S, Vellozzi C, Reingold A, et al.** Prevention of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices. *MMWR Recomm Rep* 2018; 67(1):1–31. doi:10.15585/mmwr.rr6701a1
 51. **Meites E, Szilagyi PG, Chesson HW, Unger ER, Romero JR, Markowitz LE.** Human papillomavirus vaccination for adults: updated recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep* 2019; 68(32):698–702. doi:10.15585/mmwr.mm6832a3
 52. **Feldman CH, Kim SC.** Should we target patients with autoimmune diseases for human papillomavirus vaccine uptake? *Expert Rev Vaccines* 2014; 13(8):931–934. doi:10.1586/14760584.2014.930346

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