Vaccination Guidelines for Patients with Immune-mediated Disorders Taking Immunosuppressive Therapies: Executive Summary

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ABSTRACT. The use of immunosuppressive therapies for immune-mediated disease is associated with an elevated risk of infections and related comorbidities. While many infectious diseases can generally be prevented by vaccines, immunization rates in this specific patient population remain suboptimal, due in part to uncertainty about their efficacy or safety under these clinical situations. To address this concern, a multidisciplinary group of Canadian physicians with expertise in dermatology, gastroenterology, infectious diseases, and rheumatology developed evidence-based clinical guidelines on vaccinations featuring 13 statements that are aimed at reducing the risk of preventable infections in individuals exposed to immunosuppressive and immunomodulatory agents. (J Rheumatol First Release February 1 2019; doi:10.3899/jrheum.180784)

Key Indexing Terms:
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The use of immunosuppressive therapies, including certain conventional synthetic disease-modifying antirheumatic drugs (DMARD), targeted synthetic DMARD, and biologics, has improved disease control and quality of life for patients with autoimmune and inflammatory diseases. However, because these treatments may attenuate protective immunity, some patients are potentially at an increased risk of developing common and opportunistic infections, complicated by higher rates of related morbidity and mortality than age- and sex-matched control populations[1,2,3,4]. Although this risk can

be significantly reduced with commercially available vaccines, physicians often hesitate to vaccinate these patients because of uncertainties regarding the safety and efficacy of immunization while being treated with immunosuppressive medications[5,6,7,8,9].

This executive summary of the clinical recommendations provides guidance regarding the vaccination of adults receiving immunosuppressive medications for the treatment of immune-mediated diseases (IMD), or infants with intrauterine exposure to such agents.

MATERIALS AND METHODS

A Canadian multidisciplinary committee with expertise in gastroenterology (JKM, AB, BB, AHS), dermatology (KAP, MG, RB, VH), rheumatology (BH, JEP, JW, SJ), and infectious diseases (DK, DCV) developed guidelines on the management of vaccination in patients receiving immunosuppressive therapies. Literature searches by Synapse Medical Communications identified clinical trials, metaanalyses, systematic reviews, observational studies, case series, and existing guidelines published from 2009 to 2017 across multiple databases (Embase, MEDLINE, PubMed) as per the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) system[10]. Reference lists were manually searched to identify relevant articles and included based on the committee's discretion (Figure 1). Published studies were then reviewed by the committee and assessed according to the GRADE evidence levels[10]. The quality of evidence was rated as "high" (indicating that further research is unlikely to change the confidence in the estimate of effect), "moderate" (implying that further research is likely to have an effect on the confidence in the estimate of effect), "low" (suggesting that further research is likely to have a strong effect on the confidence in the estimate of effect), or "very low" (meaning that any estimate of effect is very uncertain).

The Steering Committee [KAP (chair), JKM, DK, BH] developed the initial statements, which underwent 2 rounds of revisions according to feedback received from all authors. All 14 members voted on a Web-based

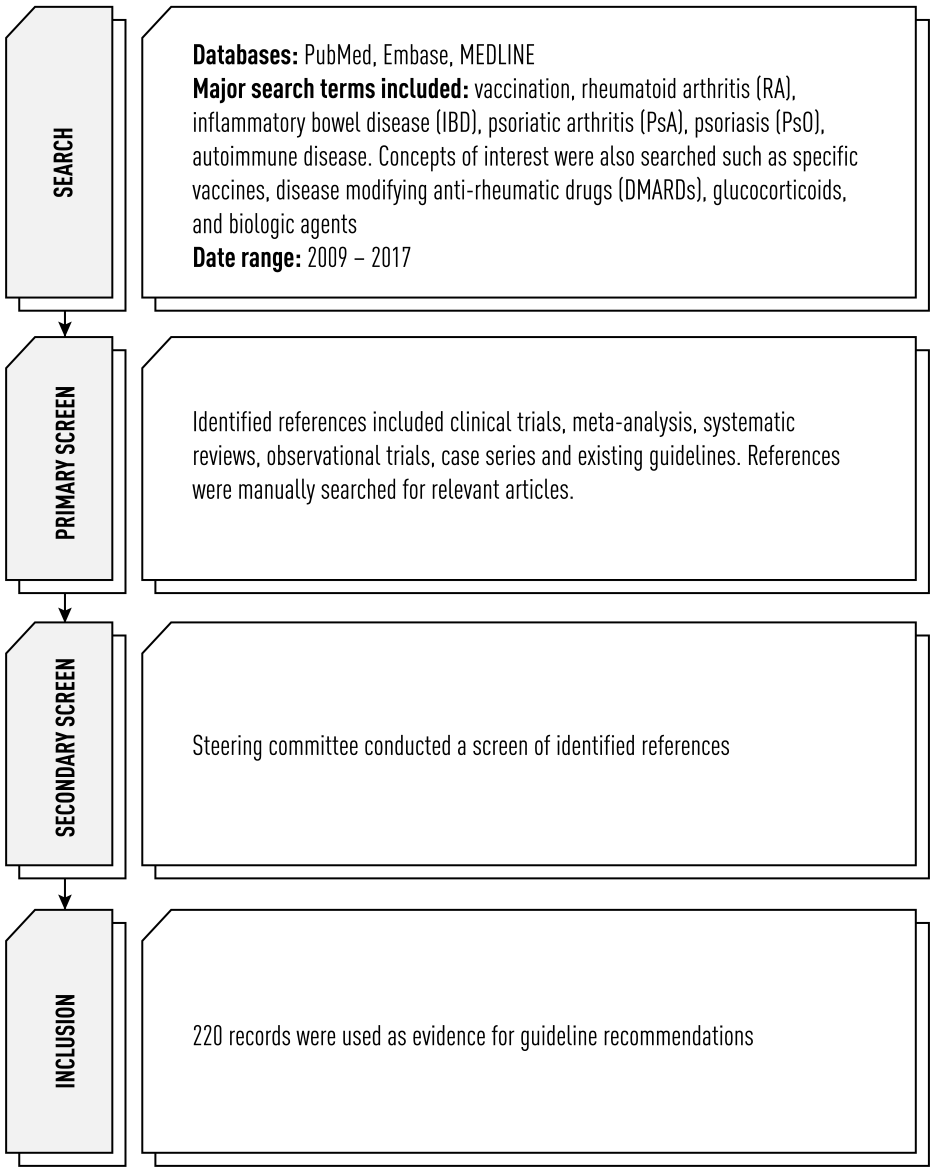

Figure 1. Literature search methodology.

platform to determine the level of agreement for each statement using a 5-point scale (strongly agree, agree, neutral, disagree, strongly disagree). Statements achieving ≥ 75% agreement were included in the guidelines. Of the 15 statements considered, 2 were rejected.

The strength of recommendations was evaluated according to the GRADE and rated as "strong" when desirable consequences clearly outweighed undesirable consequences, "conditional" when desirable consequences probably outweighed undesirable consequences, or "weak" when the balance between desirable and undesirable consequences was closely balanced or uncertain.

Table 1. Guideline statements*.

Statement	Recommendation	Evidence Level/Recommendation Strength
Statement 1	In patients newly diagnosed with immune-mediated diseases, we recommend that immunization status be assessed, and age- and condition-appropriate vaccines be administered prior to initiation of immunosuppressive treatment.	Strong recommendation, moderate-level evidence
Inactivated vaccines		
Statement 2a	To optimize the immunogenicity of inactivated vaccines in treatment-naive patients with immune-mediated conditions, we suggest that immunization be performed at least 2 weeks prior to initiation of immunosuppressive therapy, whenever possible.	Conditional recommendation, moderate-level evidence
Statement 2b	Among patients with immune-mediated diseases currently receiving immunosuppression, we recommend that immunosuppressive treatment not be interrupted for administration of inactivated vaccines.	Strong recommendation, moderate-level evidence
Statement 2c	In patients with immune-mediated diseases treated with RTX who require optimal vaccine immunogenicity, we recommend that immunization be deferred to ≥ 5 mos after the last dose and at least 4 weeks prior to the subsequent dose of RTX.	Strong recommendation, low-level evidence
Live attenuated herpes zoster vaccine		
Statement 3a	To optimize the immunogenicity of the live attenuated herpes zoster vaccine in treatment-naive patients with immune-mediated conditions, we suggest immunization be performed at least 2–4 weeks prior to initiation of immunosuppressive therapy.	Conditional recommendation, moderate-level evidence
Statement 3b	In patients with immune-mediated diseases receiving immunosuppressive agents, the live attenuated herpes zoster vaccine can be safely administered to patients at risk, but the subunit vaccine is the preferred alternative. Individual situations should be assessed for patients treated with a combination of immunosuppressive drugs, if the live vaccine is being considered.	Strong recommendation, moderate-level evidence
Other live attenuated vaccines		
Statement 4a	In treatment-naive patients with immune-mediated diseases who are vaccinated with live attenuated vaccines, we recommend that the duration of viremia following immunization be considered when determining the optimal time to initiate immunosuppressive therapy.	Strong recommendation, very low-level evidence
Statement 4b	In patients with immune-mediated diseases who interrupt immunosuppressive treatment prior to vaccination, we recommend that the duration of viremia following immunization be considered when determining the optimal time to re-initiate immunosuppressive therapy.	Strong recommendation, very low-level evidence
Statement 4c	In patients with immune-mediated diseases receiving immunosuppressive agents, we suggest that live attenuated vaccines be administered when individual benefits outweigh the perceived risks.	Conditional recommendation, low-level evidence
Statement 4d	In situations where patient safety is a paramount concern and the clinical situation allows, we suggest that immunosuppressive treatment be interrupted for a duration based on drug pharmacokinetics prior to immunization with live vaccines.	Conditional recommendation, low-level evidence
Vaccination of infants with early exposure to immunosuppressive agents		
Statement 5a	In infants exposed to immunosuppressive agents *in utero* during the third trimester, we recommend that inactivated vaccines be administered according to the local immunization schedule.	Strong recommendation, very low-level evidence
Statement 5b	In infants exposed to immunosuppressive agents *in utero* during the third trimester, we recommend that the MMR and varicella vaccines be administered according to the local immunization schedule.	Strong recommendation, low-level evidence
Statement 5c	In infants breast-fed by mothers receiving immunosuppressive regimens, we recommend that inactivated and live attenuated vaccines be administered according to the local immunization schedule without delay.	Strong recommendation, very low-level evidence

* Further information is available in the full guidelines[11]. RTX: rituximab; MMR: measles, mumps, rubella.

RESULTS

The developed guidelines consist of 13 statements addressing general immunization strategies for individuals exposed to biologic and/or nonbiologic immunomodulatory agents (Table 1)[11]. Of these, 10 statements focus on the management of adults with IMD who are considering age-appropriate primary and secondary immunizations with live or inactivated vaccines. Recommendations specifically regarding the use of the live attenuated herpes zoster vaccine are also provided. The remaining 3 statements pertain to the timing of routine childhood vaccinations in infants exposed to immunosuppressive drugs either *in utero* during the third trimester or through breastfeeding.

In the full guideline document, each statement is followed by a discussion of the supporting evidence, as well as any existing recommendations or guidance from other physician organizations or societies[11].

DISCUSSION

This document is intended to provide guidance on the vaccination of individuals exposed to immunosuppressive therapies. A robust discussion of these recommendations is provided in the full guideline document[11].

These guidelines were developed according to the best data available to date. However, the body of evidence regarding the safety and efficacy of vaccination in this patient population is small and incomplete. Therefore, clinical judgment based on a careful assessment of patient factors and the risks and benefits of vaccination should always prevail when determining the best course of action for each individual.

Regular updates to the current guidelines will be necessary as new clinical trial data and treatment options emerge.

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