Journal of the Canadian Association of Gastroenterology, 2019, 2(4), 149–152
doi: 10.1093/jcag/gwy069
Original Article
Advance Access publication 1 February 2019

OXFORD

Original Article

Vaccination Guidelines for Patients with Immune-Mediated Disorders on Immunosuppressive Therapies—Executive Summary

Kim A. Papp MD, PhD, FRCPC[1,2], Boulos Haraoui MD, FRCPC[3], Deepali Kumar MD, MS, FRCPC[4,5], John K. Marshall MD, MS, FRCPC, AGAF[6], Robert Bissonnette MD[7], Alain Bitton MD, FRCP[8], Brian Bressler MD, MS, FRCPC[9,10], Melinda Gooderham MS, MD, FRCPC[2,11], Vincent Ho MD, FRCPC[9], Shahin Jamal MD, FRCPC, MS[12], Janet E. Pope MD, MPH, FRCPC[13,14], A. Hillary Steinhart MD, FRCP(C)[5,15], Donald C. Vinh MD[8,16], John Wade MD, FRCP(C)[9,17]

[1]K Papp Clinical Research, Waterloo, Ontario, Canada; [2]Probity Medical Research, Waterloo, Ontario, Canada; [3]Centre Hospitalier de l'Université de Montréal, Montréal, Québec, Canada; [4]University Health Network, Toronto, Ontario, Canada; [5]Faculty of Medicine, University of Toronto, Ontario, Canada; [6]Department of Medicine and Farncombe Family Digestive Health Research Institute, McMaster University, Hamilton, Ontario, Canada; [7]Innovaderm Research Inc., Montréal, Québec, Canada; [8]McGill University Health Centre, Montréal, Québec, Canada; [9]Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada; [10]St. Paul's Hospital, Vancouver, British Columbia, Canada; [11]Faculty of Medicine, Queen's University, Kingston, Ontario, Canada; [12]Vancouver Coastal Health, Vancouver, British Columbia, Canada; [13]Faculty of Medicine, University of Western Ontario, London, Ontario, Canada; [14]St. Joseph's Health Care, London, Ontario, Canada; [15]Mount Sinai Hospital, Toronto, Ontario, Canada; [16]Research Institute, McGill University Health Centre, Montréal, Québec, Canada; [17]Vancouver General Hospital, Vancouver, British Columbia, Canada

Correspondence: Kim A. Papp, K Papp Clinical Research and Probity Medical Research, 135 & 139 Union Street East, Waterloo, ON, N2J 1C4, Canada. E-mail: kapapp@probitymedical.com

Abstract

The use of immunosuppressive therapies for immune-mediated disease (IMD) 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 agents.

Keywords: *Vaccination; Immunosuppression; Immune-mediated disease*

The full guidelines of this executive summary were published in the *Journal of Cutaneous Medicine and Surgery.* (Papp KA, Haraoui, B, Kumar D, Marshall JK, Bissonnette R, Bitton A, Bressler B, Gooderham M, Ho V, Jamal S, Pope JE, Steinhart AH, Vinh DC, Wade J. Vaccination guidelines for patients with immune-mediated disorders on immunosuppressive therapies. J Cutan Med Surg 2019;23:50-74.)

The use of immunosuppressive therapies, including certain common synthetic disease-modifying antirheumatic drugs (csDMARDs), targeted synthetic DMARDs (tsDMARDs) and biologics, has improved disease control and quality of life for patients with autoimmune and inflammatory diseases. However, as these treatments may attenuate protective

Received: July 11, 2018; Accepted: December 12, 2018

Table 1. Guideline statements*

	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-naïve 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 rituximab who require optimal vaccine immunogenicity, we recommend that immunization be deferred to ≥5 months after the last dose and at least 4 weeks prior to the subsequent dose of rituximab.	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-naïve 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 on 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-naïve 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 on 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 3rd 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 3rd 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 on 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

MMR: measles, mumps, rubella

*Please refer to the full guidelines for further information.

†The Centers for Disease Control and Prevention (CDC) recommends the use of the herpes zoster subunit vaccine over the live attenuated version (11).

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 (1–4). Although this risk can be significantly reduced with commercially available vaccines, physicians often hesitate to vaccinate these patients due to uncertainties regarding the safety and efficacy of immunization while on immunosuppressive medications (5–9).

This executive summary of the clinical recommendations provides guidance regarding the vaccination of adults receiving immunosuppressive medications for the treatment of IMDs 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 on immunosuppressive therapies. Literature searches by Synapse Medical Communications identified clinical trials, meta-analyses, 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 were included based on the committee's discretion. Published studies were then reviewed by the committee and assessed according to 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 impact on the confidence in the estimate of effect), 'low' (suggesting that further research is likely to have a strong impact 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 two rounds of revisions according to feedback received from all authors. All 14 members voted on a web-based platform to determine the level of agreement for each statement using a five-point scale ('strongly agree', 'agree', 'neutral', 'disagree', 'strongly disagree'). Statements achieving ≥75% agreement were included in the guidelines. Of the 15 statements considered, two statements were rejected.

The strength of recommendations was evaluated according to 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.

RESULTS

The guidelines developed consist of 13 statements addressing general immunization strategies for individuals exposed to biologic or nonbiologic immunosuppressive agents (Table 1) (11). Of these, 10 statements focus on the management of adults with IMDs 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 three 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, including the role that biologic and nonbiologic agents may play in supporting these statements (11). Any existing recommendations or guidance from other physician organizations or societies is also discussed (11).

DISCUSSION

This document is intended to provide guidance on the vaccination of individuals exposed to immunosuppressive therapies. For an in-depth review of the data and its relevance to individual medical specialities, readers are directed to the full guideline document (11).

While specialists endorse the importance of giving age- and disease-appropriate vaccines to patients with IMDs, primary care physicians (PCPs) are often tasked with carrying out immunizations in these patients. To ensure that necessary vaccines are given and that patients receive consistent care across health care providers, communication between specialists and PCPs is imperative. Should the need arise, these guidelines may serve to inform not only specialists but also family physicians and other health care providers on issues regarding the safety and efficacy of vaccines in patients with IMDs on immunosuppressive therapies.

Although these guidelines were developed according to the best data available to date, the body of evidence regarding the safety and efficacy of vaccination in this patient population remains scarce 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.

Acknowledgments

The full guidelines of this executive summary were published in the *Journal of Cutaneous Medicine and Surgery*. The authors thank Synapse Medical Communications, Oakville, Ontario, who provided medical writing assistance in the form of drafting and revising as per authors' directions and in accordance with the standards set out by

the International Committee of Medical Journal Editors. Medical writing support was funded by the Dermatology Association of Ontario. Development of the vaccination guidelines was funded by the Dermatology Association of Ontario. The authors received no financial support for the research, authorship or publication of the article.

Conflicts of Interest

The authors declare the following potential conflicting interests with respect to the research, authorship, and publication of the article: KP is an advisory board participant, steering committee member, investigator, speaker, and/or consultant for AbbVie, Akros, Allergan, Amgen, Anacor, Astellas, AstraZeneca, Baxalta, Baxter, Boehringer Ingelheim, Bristol-Myers Squibb, CanFite, Celgene, Coherus, Dermira, Dow Pharma, Eli Lilly, Forward Pharma, Galderma, Genentech, GSK, Janssen, Kyowa Hakko Kirin, LEO Pharma, MedImmune, Meiji Seika Pharma, Merck (MSD), Merck Serono, Mitsubishi Pharma, Novartis, Pfizer, Regeneron, Roche, Sanofi Genzyme, Takeda, UCB and Valeant. BH is an advisory board participant, speaker, consultant and/or investigator for Amgen, AbbVie, Janssen, Lilly, Merck, Pfizer, Novartis and UCB. DK is an advisory board participant, speaker, investigator and/or consultant for Astellas, GSK, Janssen, Oxford Immunotec, Pfizer, Qiagen and Sanofi. JKM is an advisory board participant, speaker, and/or consultant for AbbVie, Allergan, Celgene, Celltrion, Ferring, Hoffman-La Roche, Hospira, Janssen, Lilly, Merck, Pfizer, Procter & Gamble, Shire and Takeda. RB is an advisory board participant, investigator, speaker, and/or consultant for AbbVie, Amgen, Boehringer Ingelheim, BMS, Celgene, Eli Lilly, Galderma, GSK Stiefel, Immune, Incyte, Janssen, Kineta, Leo Pharma, Merck, Novartis, Pfizer and Xenoport and is a shareholder of Innovaderm Research. AB is an advisory board participant, speaker, and/or investigator for AbbVie, Janssen, Takeda, Shire, Ferring, Pfizer, Merck and Pharmascience. BB is an advisor and/or speaker for AbbVie, Actavis, Allergan, Amgen, Celgene, Ferring, Genentech, Janssen, Merck, Pendopharm, Pfizer, Shire and Takeda and received research support from AbbVie, Alvine, Amgen, Atlantic Pharmaceuticals, Boehringer Ingelheim, BMS, Celgene, Genentech, GlaxoSmithKline, Janssen, Merck, Qu Biologic, Red Hill Pharma and Takeda. MG is an advisory board participant, investigator, consultant, and/or speaker for AbbVie, Actelion Pharmaceuticals, Akros Pharma, Amgen, Arcutis, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Dermira, Eli Lilly, Galderma, GSK, Janssen, LEO Pharma, MedImmune, Novartis, Pfizer, Regeneron Pharmaceuticals, Roche, Sanofi Genzyme, Sun Pharmaceutical Industries, UCB and Valeant Pharmaceuticals. VH is an advisory board participant, investigator, and/or speaker for Abbvie, Lilly, Novartis, Janssen and Sanofi. SJ is an advisory board participant for Abbvie, Amgen, BMS, Celgene, Eli Lilly, Janssen, Merck, Novartis, Pfizer, Roche, Sandoz, Sanofi Aventis and UCB. JEP is a consultant for Lilly, Merck, Novartis, Pfizer, Roche, Sanofi, Sandoz and UCB and received research grants from Merck, Pfizer, Roche, UCB and Seattle Genetics. AHS is an advisory board participant, speaker, investigator, and/or consultant for Abbvie, Amgen, Arena Pharmaceuticals, Celgene, Ferring, Genentech, Hoffmann-La Roche, Hospira, Janssen, Merck, Pfizer, Pharmascience, Red Hill Biopharma and Takeda. DCV is an advisory board participant, speaker, consultant, and/or investigator for Cidara, CSL Behring Canada, Merck Canada and Shire Canada. JW is an advisory board participant and consultant for Abbvie, Amgen, BMS, Celgene, Janssen, Lilly, Novartis, Roche, Sanofi and UCB.

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