REVIEW ARTICLE

Autoimmune disease and vaccination: impact on infectious disease prevention and a look at future applications

Q8 JOHN E. MCKINNON, and KATHLEEN MAKSIMOWICZ-MCKINNON

DETROIT, MICH

Vaccines hold promise both for the prevention of infections and as potential immunologic therapy for patients with autoimmune disease (AD). These patients are at high risk for both common and opportunistic infections, but this risk can be significantly reduced and even obviated with the use of recommended available vaccines. Unfortunately, patients with ADs are not routinely offered or provided indicated vaccinations and have higher rates of complications from vaccine-preventable illnesses than patients without ADs. In addition, vaccine therapy is currently under study for the treatment of autoimmune disorders, with early studies demonstrating immunomodulatory effects that may counter undesired immune activation and alleviate disease activity. (Translational Research 2015;■:1–14)

Q9 **Abbreviations:** ■■■ = ■■■

Q2 INTRODUCTION

Disease-modifying immunosuppressive (IS) therapies have significantly impacted disease control and quality of life for many patients with autoimmune disease (AD). Unfortunately, both ADs and IS therapy directly alter normal immunologic function, leading to increased infection risk.[1,2] Furthermore, the newer biologic agents have been associated with a higher risk of serious infections, with a pooled odds ratio of 2.0 when compared with nonbiologic disease–modifying antirheumatic drugs.[3,4] In addition, infection risk is increased between 1.79 and 3 fold for biological agents used for IS therapy when compared with nonimmunosuppressed populations.[5-10] These data demonstrate the urgent need to provide AD patients with better prophylactic measures against infection.

Infection prophylaxis in immunosuppressed patient populations using antimicrobial chemoprophylaxis, such as measures currently used in the organ transplant and human immunodeficiency virus (HIV) populations, might be considered in other subpopulations, perhaps the most heavily immunosuppressed.[11-14] However, limited information is available to support the efficacy of these measures in most patients with ADs, with the exception of *Pneumocystis jirovecii* (PCP) prophylaxis Q3 in a small, well-defined subset of patients with ANCA-associated vasculitis.[15,16] In contrast, most

Q1 From the Division of Infectious Diseases, Henry Ford Hospital System, Detroit, Mich.

Kathleen Maksimowicz-McKinnon: New Center One, Suite 800, Henry Ford Hospital, 3031 W. Grand Blvd, Detroit, MI, 48202, USA kmckinn2@hfhs.org.

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Reprint requests: John E. McKinnon, Division of Infectious Diseases, Henry Ford Hospital, Clara Ford Suite 322, 2799 W. Grand Blvd., Detroit, MI 48202; e-mail: jmckinn3@hfhs.org.

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inactivated or killed adult vaccines have been studied and are recommended for routine administration in patients with various ADs. Vaccines play a key role in the prevention of both communicable diseases and of infections in susceptible populations.[17] In patients with AD receiving IS therapy, vaccinations are often not offered or provided for a variety of reasons, including the fear of complications or vaccine-related illnesses, a concern for disease flare or reactivation, a perceived lack of effectiveness, or a misunderstanding of current vaccine guidelines.[18] Currently, only about 20% of patients in outpatient rheumatology practices receive vaccination against both influenza and pneumococcal infections, belying the need for enhanced strategies to ensure that routine vaccinations are provided to this at-risk population.[19-21] Indeed, it has been demonstrated that vaccination rates can be improved to 80% or more by using simple strategies to increase awareness of the potential benefits and safety of vaccination in this population.[22] Several organizations support the administration of vaccines for vaccine-preventable diseases in patients with autoimmune disorders.[17,23] Ongoing research is now evaluating the use of vaccine models as a potential therapy for patients with AD, with initial studies demonstrating potentially beneficial effects on uncontrolled immune activation and disease activity. In this review, we will examine the efficacy, safety, and use of the current recommended vaccines for patients with autoimmune disorders, highlight key concepts for vaccination in this population, and introduce several evolving vaccination strategies that may represent the future treatment of immunologic diseases.

MATERIALS AND METHODS

Literature search strategy. The Medline database was searched through PubMed and Ovid, using the key words, individually and in combination with specific vaccines and autoimmune disorders (using several related disease names) including but not limited to the following: "AD," "rheumatic disease," "rheumatoid arthritis," "psoriasis," "inflammatory bowel disease," "lupus," "SLE," "systemic lupus erythematosus," "vasculitides," "ANCA-associated vasculitis," "vaccines," "vaccine outcomes," "vaccine efficacy (VE)," "immunization," "vaccination," "autoimmunity," "vaccine safety," "therapeutic vaccines," "ASIA," and "guidelines." Recommendations and guidelines regarding immunocompromised patients and immunization were obtained from the recently published ACIP 2015 guidelines, the Center for Disease Control recommendations for vaccination, and scientific society's Web sites (ACIP, CDC, EULAR and ACR) and their publications. The reference lists of retrieved articles were searched for relevant publications. We reviewed articles published primarily in English or Spanish and selected relevant clinical trials when available for each area publications were reviewed from 1979 to the present to include both pertinent historical and contemporary data. No patient information was directly accessed; hence, institutional review board's review and approval were not required for this article and review.

Available vaccines. There are currently vaccines recommended for routine administration in patients with AD that are safe and efficacious. Inactivated, killed, subunit, or toxoid immunizations do not carry any risk of infection attributable to reactivation or dissemination of the vaccine agent and are uniformly safe for patients requiring any degree of IS therapy (only excluding those with known allergies to vaccine components). These vaccines serve to elicit the formation of active immunity by the induction of antigen-specific antibodies. Inactivated/killed or toxoid vaccines include the Q4 influenza (inactivated), hepatitis A and B, and tetanus/reduced diphtheria toxoid/acellular pertussis vaccines (Tables I and II). These vaccines are designed to induce both B- and T-cell immune responses. Most of the killed or attenuated vaccines are considered to provide transient immunity as the immune response generated is limited, weaker, and less likely to be sustained when compared with live vaccines, which induce a broader, intense, and durable response.[24]

Live vaccines consist of attenuated wild-type pathogens such as influenza virus or varicella zoster virus (VZV; Table II).[24,25] These vaccines are generally not recommended for patients receiving moderate or intensive IS therapy. Live vaccines carry the risk of dissemination of the attenuated virus and potential for the reemergence of its natural virulence in an immunosuppressed host. As previously stated, these vaccines are more immunogenic and lead to a more persistent response directed against the target pathogen.[25]

Live vaccines are currently safely used in other immunosuppressed populations (eg, mumps, measles, rubella [MMR] and varicella in HIV seropositive patients with $CD4^+$ T-cell counts above 200 cells/mm^3), suggesting that this area may warrant further consideration and study in other immunosuppressed populations.[17,25-28]

Vaccine safety. Vaccine safety has been extensively evaluated in diverse populations, using clinical trials, cohort studies, and postmarketing surveillance.[29-35] Three active systems evaluate and assure vaccine safety: the Vaccine Adverse Event Reporting System; the Vaccine Safety Datalink; and the Clinical Immunization Safety Assessment Network.[24,32,34] Adverse events from vaccination are rare in both children and adults and are reported to the Vaccine