



Review

Influenza and pneumococcal vaccinations of patients with systemic lupus erythematosus: Current views upon safety and immunogenicity



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ABSTRACT

Systemic lupus erythematosus (SLE) is a chronic immune-mediated inflammatory multisystem disease. The onset of viral and bacterial infections may favor the exacerbation of the disease, amplify autoimmune processes and contribute to mortality and morbidity. The prevention of influenza and *Streptococcus pneumoniae* infections with vaccination should receive particular attention in SLE patients considering their elevated incidence, their high attack rate in epidemic periods, their potentially severe complications as well as the immunocompromised state of the host. The use of non-adjuvanted vaccine preparations should be preferred in order to avoid the onset of the “Autoimmune (auto-inflammatory) Syndrome Induced by Adjuvants” or “ASIA”. In this review, we report that influenza and pneumococcal vaccinations in SLE patients are: 1) recommended to reduce the risk of development of these infections; 2) strongly suggested in elderly subjects and in those receiving high dose immunosuppressive treatments; 3) efficacious, even if specific immune responses may be lower than in the general population, as generally the humoral response fulfills the criteria for vaccine immunogenicity; and 4) safe in inactive disease although may favor a transient increase in autoantibody levels and rarely disease flares.

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1. Introduction

Systemic lupus erythematosus (SLE) is a chronic inflammatory multisystem disease with distinct clinical and laboratory features. The disease is characterized by a variable clinical course. Indeed, while in some patients the disease may be mild affecting only one organ system, in others it is manifested by severe central nervous system, renal and other vital organs involvement [1]. The treatment of SLE includes the use of nonsteroidal anti-inflammatory and anti-malarial drugs, corticosteroids and immunosuppressive agents [1]. However, several SLE patients are refractory to conventional treatments [2–4]. Thus, therapies targeting B-cells, T-cells, T/B cell interaction, cytokines and complement are at forefront of new treatments [2,5–10]. The pathogenesis of SLE involves a complex interplay between genetic and environmental factors and the adaptive and innate immune systems [2,11]. Therefore, it has been proposed that the pathogenesis of SLE is represented by a “galaxy” of different pathogenic events requiring both a polyvalent therapy to control the disease and new therapeutic approaches [2,12]. Defects in central and peripheral tolerance, increased antigenic load, excess T-cell help, B-cell hyperactivity, autoantibody production and cytokine imbalance, ultimately lead to immune-complex formation and complement activation causing immunologically mediated tissue injury and disease onset [2,13,14]. The association between infections and SLE is of great interest. SLE patients may develop common bacterial opportunistic infections particularly of the respiratory and urinary tracts. Infections may trigger autoimmunity and possibly have a pathogenic role in the development and exacerbation of the SLE contributing to the mortality and morbidity of the disease [15]. Notably, infections represent one of the primary causes of death among SLE patients [16]. Regardless of the cause of infections, adequate and prompt recognition and proper treatment of the infected patient are imperative. In the past years, substantial progress has been made in the treatment of chronic rheumatic and autoimmune diseases such as rheumatoid arthritis (RA), SLE, ankylosing spondylitis (AS), psoriasis (Ps) and/or psoriatic arthritis (PsA), and granuloma annulare [2,17–21]. Corticosteroids and conventional immunosuppressive drugs are widely used for the treatment of SLE patients. However, patients refractory to the conventional regimens can be given effective therapy with the newer “biological” agents [2,17–21]. Among the “biological” agents, tumor necrosis factor (TNF)- α inhibitors

have demonstrated efficacy in large, randomized controlled clinical trials either as monotherapy or in combination with other anti-inflammatory or disease modifying anti-rheumatic drugs (DMARDs) for the treatment of the above mentioned immune-mediated diseases [2,17–21]. Notably, TNF- α is a proinflammatory cytokine known to have a central role in the initial host response to infection [2,17–21] and in the pathogenesis of the above mentioned chronic immune-mediated diseases [2,17–21]. The risk of infection is also dependent on the degree of immunosuppression associated with DMARDs, most of which also have cytostatic effects favoring leukopenia [22–24]. Furthermore, corticosteroids are often used together with DMARDs increasing their cytotoxic effects. The “biological” drugs such as TNF- α inhibitors are also used in association with DMARDs and amplify the immunosuppression by additional lymphocyte toxicity and inhibition of important cytokine, such as TNF- α , and noncytokine activation pathways [2,17–21]. Thus, patients with SLE, particularly the elderly subjects (age ≥ 65 years) when receiving high corticosteroid doses, DMARDs and “biological” drugs, may be at increased risk of influenza and *S. pneumoniae* infections which can cause pneumonia, septicemia and meningitis [2,25,26]. The prevention of influenza and *S. pneumoniae* infections with vaccination should receive particular attention considering the danger coming from the annual possible stimulation of a dysregulated immune system, the high attack rate in epidemic periods as well as the potentially severe complications [26,27]. Despite the evidence presented, vaccination rate of SLE patients is low [26,28,29]. Traditional arguments against vaccination include reactivation of the disease, insufficient response and vaccination side-effects [30,31]. In this review, we report the recommendation to influenza and pneumococcal vaccinations, and we discuss the efficacy and safety of these vaccines in SLE patients.

2. Influenza viruses

Influenza A subtypes that are generated by a major genetic reassortment (i.e., antigenic shift) or that are substantially different from viruses that have caused infections over the previous several decades have the potential to cause a pandemic [32]. A novel swine influenza A(H1N1) virus that clinically mimics seasonal influenza was identified in two children in the United States in March and April 2009 [33,34]. When the transmission seemed to persist and increase in the Northern Hemisphere during the autumn and winter 2009, the World Health Organization (WHO) immediately proclaimed a worldwide pandemic, characterized by uncontained community level transmission of the A(H1N1) virus in multiple areas of the world [35]. Data from epidemiologic studies conducted during the 2009 influenza A (H1N1) pandemic indicate that the risk for influenza complications among adults aged 19–64 years who had 2009 pandemic influenza A (H1N1) was greater than typically occurs for seasonal influenza [36]. The elderly subjects, the obese and pregnant women and those individuals with chronic diseases may develop acute respiratory distress syndrome or septicemia requiring admission to intensive care units [37–41]. Influenza viruses also undergo frequent antigenic changes as a result of point mutations and recombination events that occur during viral replication (i.e., antigenic drift). For these reasons, influenza vaccines do not provide lifelong protection over the years and vaccines should be updated annually to maintain their effectiveness. The influenza vaccination recommendations are reported in Table 1. The frequency of influenza infection among patients with SLE has not been estimated. While prevention of influenza infections may reduce the risk of development of pneumonia, there has

Table 1
Influenza vaccination recommendations.

- ✓ All individuals aged 6 months–4 years
- ✓ All individuals aged ≥ 50 years
- ✓ Chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, neurologic, hematologic, or metabolic diseases (including diabetes mellitus)
- ✓ Immunosuppressed subjects (including immunosuppression caused by drugs or by human immunodeficiency virus infection)
- ✓ Individuals who are or will be pregnant during the influenza season
- ✓ Children aged 6 months–18 years and receiving long-term aspirin therapy and who therefore might be at risk for experiencing Reye syndrome after influenza virus infection
- ✓ Residents or nursing homes and other chronic-care facilities
- ✓ American Indians/Alaska Natives
- ✓ Obese (body-mass index ≥ 40)
- ✓ Health-care personnel
- ✓ Household contacts and caregivers of children aged <5 years and adults aged ≥ 50 years, with particular emphasis on vaccinating contacts of children aged <6 months
- ✓ Household contacts and caregivers of persons with medical conditions that put them at higher risk for severe complications from influenza

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