

Prevention of Infection in Lupus Patients

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Abstract

Despite the many advances in the treatment of systemic lupus erythematosus (SLE), infection remains one of the leading causes of morbidity and mortality of patients. The reasons for the high incidence of infection are immunosuppressive therapy and immune disturbances of lupus itself. Bacterial infections are most frequent, followed by viral and fungal infections. Vaccination is the most important tool in the prevention of infections specially influenza and Streptococcus pneumonia infections. Prophylaxis of tuberculosis and pneumocystosis are also recommended to prevent those deadly infections. In this review, we aim to give an overview of the prevention means of infections in SLE.

Keywords: Lupus; Infection; Vaccination; Chemoprophylaxis

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease, characterized by dysregulation of the innate and adaptive immune systems, production of autoantibodies, and tissue damage resulting from chronic inflammation [1,2]. The treatment includes the use of non-steroidal anti-inflammatory and anti-malarial drugs, corticosteroids and immunosuppressive agents [3]. Despite great improvements in reducing mortality in SLE, the mortality due to infections remains unchanged, constituting the cause of death in 1 out of 3 SLE patients [3-5]. Multiple risk factors for infection have been reported. They include immunological disorders due to lupus and its therapy, particularly immunosuppressive and cytotoxic medications [5,6]. Lupus disease activity, measured by the SLE disease activity index (SLEDAI), is also an important risk factor for infection [7]. The risk is also dependent on the degree of immunosuppression [8-10]. SLE patients may develop common bacterial opportunistic infections particularly of the respiratory and urinary tracts [3]. Opportunistic infections such as pneumocystis (PCP) are associated with mortality as high as 46% [5,6]. Debilitating viral infections, such as herpes zoster and cytomegalovirus (CMV), are also seen at significantly higher rates in patients with SLE [11]. In this review, we aim to give an overview of the prevention means of infections in SLE.

How to Reduce the Risk of Infectious Complications in Patients with SLE?

Vaccine recommendations

Vaccination is the most important tool in the prevention of infections in SLE patients [12]. The European league against rheumatism is recommended that patients with LES receive vaccinations within a period of clinical remission [13,14]. Non-live vaccines can be administered independent of medication use. Inactivated live vaccines are best avoided in patients receiving immunosuppressive agents, including glucocorticoids at daily doses over 20 mg. Live vaccines are contraindicated in SLE patients with

active disease or on high-dose immunosuppressive therapy as they can result in infection [13,15-17]. Many vaccines, including HPV, hepatitis B, pneumococcal vaccine, and influenza vaccine, have been shown to be immunogenic in the SLE population [18]. Although these vaccines have found to be generally safe and well tolerated by SLE patients, lupus-like syndrome and other autoimmune phenomena such as induction of lupus anticoagulants, anti-Ro/La and anti-smith antibodies have been reported following various immunizations [16]. Likewise, vaccinations may be less efficacious in SLE patients, as they have reduced primary and secondary immune responses upon antigenic challenge, in part due to immunosuppressive therapy [17,18].

Influenza vaccination

The prevention of influenza infections with vaccination (trivalent-inactivated) 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 [19]. Yearly influenza vaccination is recommended for all SLE patients; however, they may experience less protection. Adequate vaccine responses to influenza A and B, occurred in 39-41% of SLE patients compared to 71-94% controls, particularly in patients with higher ANA titers, IFN- α production, and number of ACR criteria for SLE (>6) [20,21]. Vaccination may be contraindicated during disease flare, as patients are less likely to develop a protective response [4]. While prevention of influenza infections may reduce the risk of development of pneumonia, there has been a concern that influenza vaccine may trigger SLE flares [22]. Several cases of SLE precipitation have been reported after immunization [23]. Nevertheless, most SLE patients with quiescent disease do not show an increase in both clinical and laboratory parameters after influenza vaccination as shown by the stability of SLE Disease Activity Index (SLEDAI) score [24,25].

Pneumococcal vaccination

Streptococcus pneumoniae infections are an important cause of morbidity and mortality worldwide particularly when subjects receiving aggressive long-term immunosuppressive therapy [26,27]. The 23-valent polysaccharide pneumococcal vaccine is recommended

in all SLE patients, as there is an increased risk of invasive pneumococcal infections, especially in patients with hyposplenism [4,13].

It seems not to favor the clinical exacerbation of SLE [28]. The response rate of SLE patients to pneumococcal vaccination is only 47%. Patients with high disease activity or using high dose corticosteroids were more likely to have inadequate vaccination responses. Poor responders can be vaccinated up to every 6 years as needed [4].

Human Papilloma Virus (HPV) vaccination

Given the increased risk of persistent HPV and developing abnormal cervical smears and squamous intraepithelial lesions of the cervix in SLE patient compared to healthy females, the HPV vaccine this vaccination should be encouraged [14,29]. It is a quadrivalent recombinant vaccine against HPV types 6, 11, 16 and 18.

It has been considered safe and well tolerated in a series of adolescents and young women with SLE, with no increase in mean SLEDAI scores [16,30]. Some cases of new-onset SLE in patients or disease flare have been reported two to four months following Gardasil vaccination. There are case reports of a temporal association of SLE onset or flare following Gardasil [31].

Varicella Zoster Virus (VZV) vaccination

Zostavax is a live-attenuated vaccine to prevent VZV in patients previously exposed to the virus [32,33]. The vaccine is thought to be safe, as it does not introduce new virus into a naive population, as seropositivity to VZV is confirmed prior to vaccination in immunosuppressed individuals [34]. Lupus patients with quiescent or low disease activity may benefit from Zostavax immunization, but caution should be taken by confirming prior infection with varicella-specific IgG and delaying vaccination in patients with moderate to severe disease activity and/or on high doses of corticosteroids [34].

Hepatitis B Virus (HBV) vaccination

The HBV vaccine, non-live composite vaccine, has been studied in this population as well [14]. It may be administered according to the individual risk of acquiring this infection [13]. It is recommended in a three-dose series. SLE patients have reduced seroconversion, with adequate responses in 80% of children and 93% of adults, compared to 100% of controls [35,36].

Some cases of new-onset SLE occurring within 2 months of HBV vaccination were reported [36]. In patients in whom rituximab treatment is planned, Ig levels should be tested before administration. If low baseline levels are detected, they should be monitored periodically, particularly in those at high risk, such as elderly patients or those undergoing concomitant glucocorticoid treatments [37].

Others vaccines

Other vaccinations required in SLE patients and all adults include tetanus toxoid in combination with diphtheria (Td) with a one-time acellular pertussis booster (Tdap) for all adults. SLE patients have reduced seroconversion rates (46% of recipients) and reduced antibody titers when compared to healthy controls [4].

Chemoprophylaxis

Prophylaxis of tuberculosis (TB)

Routine testing is recommended before glucocorticoids and immunosuppressive agents are used in patients coming from endemic areas [38]. Prophylaxis with isoniazid (INH) is controversial because the effectiveness of INH in preventing TB development is not well established in lupus patients, whilst INH has potential liver toxicity, especially if combined with other hepatotoxic drugs like azathioprine or methotrexate [39]. In addition, Bacillus Calmette-Guerin (BCG) vaccination has not proved effectiveness in preventing TB in adults and may be associated with adverse effects and therefore should be avoided in immunosuppressed patients [13]. However, Patients with prolonged glucocorticoid therapy and with a positive screen for latent TB should be treated with INH. Hepatic function must be closely monitored in these patients [40].

Prevention of pneumocystis (PCP)

PCP is greatly feared complication of immunosuppression [41]. Previous studies indicate that a dose of glucocorticoids 16 mg increases the risk of PCP in non-HIV individuals and reported a PCP prevalence of 0.16% in SLE patients on cyclophosphamide [11,42]. Because of the risk of serious adverse events associated with antimicrobial prophylaxis for PCP, it is recommended that prophylaxis only be used when the risk of PCP in SLE patients with CD4+ T cell count <250/ μ l, interstitial pulmonary fibrosis, high SLEDAI, severe nephritis, or with chronic use of prednisone \geq 20 mg/day [43,44].

Antimalarial drugs

Use of antimalarial drugs, including chloroquine and hydroxychloroquine, were shown to reduce incidence of infections in lupus [45]. SLE patients taking antimalarials are 16 times less likely to develop a major infection [46,47]. SLE patients who require more potent medications (corticosteroids or cytotoxic drugs) may still benefit from antimalarials, as they reduce infection rate, mortality, and have few side effects [4].

Other preventive measures

Antibiotic prophylaxis to prevent bacterial endocarditis is recommended prior to invasive dental procedures, as 1-4% of SLE patients develop endocarditis, a rate higher than patients with prosthetic heart valves [48]. Regardless of the cause of infections, adequate and prompt recognition and proper treatment of the infected patient are imperative [3]. Empiric therapy should be initiated for suspected bacterial infection, covering the most common and most deadly pathogens. Empiric antibiotic therapy in SLE patients with suspected bacteremia should include coverage of community-acquired causes (*E. coli*, *S. aureus*, *Salmonella*), as well as nosocomial causes (*Pseudomonas*, *Klebsiella*, *Acinetobacter*), as they are associated with reduced survival and poor long-term outcomes [49].

The use of glucocorticoids should be limited as much as possible, both in terms of daily dose and duration, with avoidance of long-term doses higher than 5 mg/day, which are clearly related to many serious side effects, including infections [50]. Early identification of infections precipitating or coinciding with disease flare is essential, as a delay in antimicrobial therapy results in worse outcomes in SLE patients with infections. Procalcitonin (PCT) has a good negative predictive value

for bacterial infection in SLE patients with active disease, with a value <0.17 ng/ml ruling out infection complicating SLE flare [4]. In SLE patients with quiescent disease, an increase in the CRP level is a preferred over PCT [7].

Conclusion

Infections represent the main cause of death in patients with SLE. Many infections of them can be prevented with timely immunization, reducing exposure to contagious contacts, screening for latent infection, and minimizing exposure to immunosuppressive drugs, which are essential to achieve optimal control of SLE activity. These measures will help to reduce the burden of major infections in SLE patients and consequently improve patient outcomes.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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