*Review paper*

# Efficacy of vaccination in connective tissue diseases: systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) – review of the literature

*ANNA SIKORA*

Department of Pediatric Propedeutics, Institute of Pediatrics, Medical University, Łódź, Poland

***Abstract***

*Vaccination had been perhaps the most important achievement in medicine of the last century. Infections are one of the leading causes of morbidity and mortality in patients with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Prevention of infections in these patients is a priority. However, the safety and immunogenicity of the currently avaible vaccines in SLE and RA patients remain controversial. Recommendations for the immunisation in such patients are unclear. This article is a review of the literature focused on the outcome of immunization of known SLE and RA patients.*

***Key words:*** *vaccination, systemic lupus erythematosus, rheumatoid arthritis*

*(Centr Eur J Immunol 2004; 29 (1): 35-38)*

## Introduction

Infections are one of the leading causes of morbidity and mortality in patients with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) [1, 2]. Bacterial pathogens are the most common cause of infections [2]. Patients with SLE and RA have a higher infection rate than the general population. It is estimated that at least 50% of SLE patients will suffer a severe infectious episode during the course of the disease [3]. In cohort of 266 SLE patients, followed up for over 20 y, infection accounted for 23,3% of the 30 deaths observed and was the leading cause [2]. Prevention of bacterial infection, which is leading cause of morbidity in these patients, is priority. Although there has been significant improvement in the survival of SLE and RA patients as a result of therapy it is important to mention the fact that the most of these patients are at increased risk of to develop infectious diseases, due to both the disease itself and secondary to immunosuppresive therapy. Vaccinations may improve the survival of patients with SLE and RA.

However, it has been suggested that immunization with various vaccines may be associated with activation of autoimmune mechanism [4-7]. There are two issues regarding vaccination of these groups of patients:

1) will the vaccination of immuno-suppressed patient give a immune response and protection from the disease?

and/or

2) will vaccination trigger an escalation in the disease?

This aricle is focused on the outcome of immunization of known SLE and RA patients.

The problem mentioned in the second question was discussed in a separate study entitled „Safety of vaccination in connective tissue diseases", which has been published in the periodical „The Polish Archives of Internal Medicine" [2004, CXII, 2(8)].

Recommendations for the immunisation in patients with SLE and RA are unclear in many rheumatology textbooks. The United Kingdom Department of Health guidelines state that administration of live, attenuated vaccines to individuals receiving high dose corticosteroids (defined as prednisolone 2 mg/kg/d for children or 40 mg/d or more for adults) should be postponed for at least three months after immunosuppresive

Correspondence: Anna Sikora, MD PhD, Sporna 36/50, 91-738 Łódź, Poland. Phone/fax number: +48 42 617 77 15

treatment has been stopped or three months after levels have been reached that are not associated with immunosuppression Live attenuated vaccines include measles, mumps, rubella, polio and bacille Calmette-Guerin (BCG) [8]. Inactivated vaccines such as pertussis, vaccines which contain immunising components such as influenza and pneumococcus and toxoid such as tetanus and diphteria are generally regarded as safe in immunocompromised individuals [8]. The British Society of Rheumatology (BSR) Clinical Affairs Committee have recently proposed quidelines for vaccination in immunocompromised patients with a rheumatic disease being treated with a cytotoxic immunosuppressant and/or steroids. These quidelines are in general agreement with the Department of Healt`s general quidelines but define low dose from 20 mg/d and not 40 mg as previously accepted [8].

The respone to immunisation in SLE and RA patients remains controversial, with serum antibody titers variously reported as normal, diminished or enhanced [9-13]. This discrepancy in part may be ascribed to differing methods employment. Protective antibody levels are a more important clinical measure of immunization response than a 2-, 3-, or 4-fold increase in antibody level after vaccination [14, 15].

## Vaccination in SLE and RA patients

### Anti-pneumococcal vaccine

Immunogenicity of the pneumococcal vaccine in SLE and RA patients remains controversial. Although pneumonia is a leading cause of death in these patients, pneumococcal vaccination is not routinely recommended for immunization of patients with a connective tissue disease. Indeed patients with SLE who have undergone a splenectomy (or autosplenectomy) are at risk of fulminant pneumococcal sepsis [16]. Impaired humoral immunity, including hypocomplementemia, may underlie this predisposition [17, 18]. Patients with antiphospholid antibodies are at particularly high risk for developing pneumococcal infections [19]. The pneumococcal vaccine should be given promptly when the diagnosis of autosplenectomy is established, although the patients who are most susceptible to atypical pneumococcal infections may not respond optimally to the vaccine [20, 21].

Uthman et al. reported on autosplenectomy in SLE patients in 1996. They described in *The Journal of Rheumatology* 2 patients with irreversible SLE autosplenectomy who received pneumococcal 23-valent vaccination and and did not developed *Streptococcus pneomoniae* sepsis over followup of 12 years and 5,5 years respectively. Despite risk factors (eg. prolonged immunosuppressive therapy), pneumococcal infection did not occur, suggesting the efficacy of the pneumococcal vaccine antigens. Current recommendations also include revaccination if more than 6 years has elapsed since initial vaccination [22]. Findings of Uthman et al. confirm those of Battafarano et al. that the 23-valent pneumococcal vaccine is an important and safe preventive measure for SLE patients. In this study, Battafarano et al. determined the safety and efficacy of 3 clinically relevant vaccines in patients with SLE. They prospectively evaluated the humoral immune response of 73 SLE patients immunized with pneumococcal, tetanus toxoid (TT), and *Haemophilus influenzae* type B (HIB) vaccines. [14]. The majority of these developed protective antibody to tetanus toxoid (TT) (90%) and HIB (88%). Although protective antibody levels was not determined for pneumococcus, almost half of the patients (47%) developed a 4-fold antibody response. There was a trend toward a lower antibody response in patients with higher disease activity (measured by SLEDAI) treated with immunosuppresive therapy, though this did not reach statistical significance. In general, SLE patients with higher disease activity scores were receiving more immunosuppresive therapy. Overall lupus disease activity was unaffected by immunization. Only 6 patients in this large study developed a mild increase in SLE disease activity scores. However it is not able to determine whether a decreased antibody response is secondary to disease activity alone, or if it is a reflection of significant immunosuppressive drug therapy in patients with multiple organ involvement. Battafarano et al. concluded that patients should receive immunizations according to the recommendations of the Centers for Disease Control and Prevention and the Immunization Practices Advisory Committee. Elkayam et al. evaluated the currently available pneumococcal vaccine in both SLE and RA patients [23]. They founded that pneumococcal vaccination was immunogenic in the majority of the patients. Most of the RA and SLE patients had mild to moderate disease activity before vaccination. One month after vaccination, patients in both groups had significant increases in geometric concentrations of pneumococcal polysaccharide-specific IgG to all 7 serotypes tested, compared with prevaccination levels. Immune responses at 1 month did not differ significantly between the RA and SLE groups and were similar to those seen in the group of control subjects. However, 14 (33.3%) of 42 patients with RA and 5 (20.8%) of 24 patients with SLE responded either to none or to only 1 of 7 polysaccharides. In contrast, none of the control subjects failed to respond to pneumococcal vaccination. Poor vaccine response was not significantly associated with laboratory tests, measures of disease activity and levels of vitamin B12 or folate or use of any immunosuppressive agents including prednisone, methotrexate, hydroxychloroquine, or azathioprine. However, the mean dose of corticosteroids for RA patients was<10 mg/day, and only 1 patient was treated with a more potent immunosuppressive drug (cyclophosphamide). Thus, the effects of high-dose corticosteroids or potent immunosuppressive drugs on the ability of RA patients to respond to pneumococcal vaccination remains to be determined. Some authors have been described a decreased antibody response to immmunization in patients with rheumatic disease requiring immunosuppressive therapy [24]. In this study O`Dell et al. reported preliminary findings that

immune responses to pneumococcal vaccination were significantly decreased among RA patients who were being treated with methotrexate.

### *Influenza vaccine* in SLE

The immunogenicity of vaccines in patients with SLE has long been a matter of controversy. Lower influenza titers of antibody to influenza virus in patients with serologically active disease have been reported to be significantly lower than those in other SLE patients and in healthy control subjects [25]. In addition, a lower response in SLE patients with active nephritis or renal failure has been reported [26, 27]. In other studies the response to immunisation was good [10, 11]. In vitro study of peripheral blood mononuclear cells was found a reduced antibody response to influenzae vaccination in 28 patients with SLE [9]. In conclusion, influenza immunization is deemed effective in lupus patients. It is recommended not to immunize patients with active disease and those who are under immunosuppressive therapy (glucocorticoids or other) should not be immunized with live vaccines, but only with killed/inactivated ones [8].

### *Hepatitis B vaccine*

Very little evidence exists for determing the efficacy of hepatitis B vaccination in patients with SLE and RA. It is yet to be determined whether the immune response is impaired by active disease or immunosuppressive therapy. In one study 23 paediatric dialysis patients with SLE were vaccinated with hepatitis B vaccine and all failed to seroconvert [28]. However, a lower response to hepatitis B immunisation has been reported in patients with renal failure of any cause. Our own study in 1998-1999 y was aimed to assess efficacy of hepatitis B vaccination in 34 children with juvenile chronic arthritis (JCA) [29]. They were vaccinated with the recombinant HBV vaccine (Engerix-B) according to the scheme 0-1-6. Most of them had mild to moderate disease activity before vaccination. Very low response (no antibodies or values below 10 IU/L) was observed in 10 children, which necessiated administration of a double vaccine at 3. vaccination. All of these developed protective antibody after the 3. dose of vaccine.

Since the relative risk of occurrence of rheumatic complaints following hepatitis B vaccination is not or is slightly increased compared to general population, the morbidity and mortality that can be prevented by immunization against hepatitis B outweight by far the risk of possible adverse events [30].

## Conclusions

1. Patients on immunosuppresive agents and or high dose steroid (more than 20 mg/d) should not receive live vaccine
2. Most patients will mount a satisfactory immune response to immunisation though this may not be qualitatively the same as healthy controls.
3. It remains uncertain whether active disese and/or immunosuppression impairs the immune response to immunisation. Large studies, preferably multicentre, would help clarify this issue.
4. Response to immunization appears to be most optimal in patients with SLE and RA with less disease activity and minimal immunosuppressive therapy.

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