

Why Have Rheumatologists Been Reluctant to Vaccinate Patients with Systemic Lupus Erythematosus?



Patients with systemic lupus erythematosus (SLE) have multiple immunological abnormalities, including B cell hyperactivity, hypergammaglobulinemia, increased production of autoantibodies, and T cell dysfunction with abnormal cytokine production¹. It has been suggested that all these immunological changes are due to a defect in eliminating self/reactive T cells or B cells.

Infection is a major cause of morbidity and mortality in patients with SLE, therefore the prevention of viral and bacterial infection is very important. Patients with lupus are prone to infections due to the immunological abnormalities of the disorder itself or to the frequent use of corticosteroids and/or immunosuppressive drugs. For this high-risk population, vaccination might be useful, provided the vaccine produces protective antibodies (for example, seroconversion or ≥ 4 -fold rise in titer) without inducing autoimmune disease, increasing preexisting autoantibodies (anti-DNA, anti-Sm, anti-RNP, anti-Ro), or flaring the underlying rheumatic disease.

In 1976, the National Influenza Immunization Program in the US caused clinicians to reexamine the possible benefits and risks of influenza vaccination in patients with SLE. Because viral infection has long been postulated to play a role in autoimmune disease, rheumatologists believed that vaccination in patients with SLE might trigger autoantibody production or increase disease activity.

In 1978 and 1979, US researchers first reported on the safety, lack of induction of autoimmune phenomena, and serum protective antibody concentrations following univalent or bivalent influenza vaccination in patients with SLE who either were in remission or had a mild to moderate disease activity²⁻⁶. The serum hemagglutination-inhibiting antibody titers to influenza antigens were measured before and 4 and 8 weeks after vaccination. Protective antibody titers were defined as a ≥ 4 -fold rise in titer, although that does not give a true indication of the functional capacity of these antibodies, particularly their opsonizing activity. However, no validated disease activity measure was used.

At that time, the safety and immunogenicity of 14-valent pneumococcal vaccine was also reported in a controlled trial⁷ and later extended by other investigators⁸⁻¹⁰. The mean antibody levels were lower at both 1 month and 1 year after vaccination in 38 patients with SLE than in healthy controls. A study examined the persistence of pneumococcal antibodies in

19/38 patients with SLE at 1, 2, and 3 years after immunization and compared to 5 healthy subjects vaccinated at the same time. The mean levels in the 19 patients with lupus were lower in all 3 years, but the difference was significant at only the first year. At 3 years, only 8/19 patients had protective antibodies. No significant changes in anti-DNA were present. Another study demonstrated that antibody responses were unaffected by immunosuppressive drugs.

FROM SINGLE TO MULTIPLE SIMULTANEOUS VACCINES

In 1998, Battafarano, *et al*¹¹ demonstrated the safety and efficacy of simultaneous administration of pneumococcal, tetanus toxoid (TT), and Haemophilus influenzae type B (HIB) vaccines in 73 consecutive patients with lupus. Disease activity [SLE Disease Activity Index (SLEDAI) and Lupus Activity Criteria Count (LACC)] scores were evaluated prevaccination and 12 weeks after vaccination. Most of these patients developed protective antibody levels to at least one vaccine, disease activity was unaffected by vaccination, and antigen-specific antibody response was lower in patients with active disease receiving immunosuppressives, but this was not statistically significant.

Shortly thereafter, I conducted a study involving 12 patients with lupus who concurrently received 23-valent pneumococcal and HIB conjugate vaccines¹². HIB conjugate vaccine contains 20 μ g of tetanus protein. All patients were taking oral prednisone (mean 18.1 mg, range 5–50 mg per day) at the time of vaccination. Anti-DNA antibodies, C3 complement, serum IgG levels, Mex-SLEDAI score, and antibodies against pneumococcus and 4 serotypes as well as HIB vaccine and tetanus protein were assessed at baseline and at 4 weeks. Significant increases occurred in antibody levels to vaccines and to all 4 serotypes tested as well as tetanus protein after vaccination. Decreases in Mex-SLEDAI score and serum IgG level were seen, while C3 level increased significantly. No changes in anti-DNA antibodies were noted. The vaccines were well tolerated, and no serious adverse events were recorded. To further assess the persistence of antibodies against pneumococcal vaccine, serum samples of 9 patients were obtained at 8 months; none had protective antibodies. Other reports also confirmed the safety and immunogenicity of polyvalent pneumococcal vaccine in patients with SLE¹³⁻¹⁵.

Beginning in the new century, studies related to influenza virus vaccination in adult and child patients with SLE appeared¹⁶⁻¹⁸. In the first study, Abu-Shakra and coworkers¹⁶ showed the safety of vaccination in 24 patients using SLEDAI scores, and recommended that patients with lupus should be encouraged to receive the vaccine. In December 2002, Abu-Shakra, *et al*¹⁷ showed that specific antibody response was lower than in adults in the general population, in particular among older patients and those treated with cytotoxic drugs. In the third study, Abu-Shakra, *et al*¹⁸ examined effects on generation of autoantibodies following influenza vaccination. They found that influenza vaccination may trigger the generation of autoantibodies, although this was not clinically significant.

In the fourth study, Greek researchers¹⁹ showed that influenza vaccine generated a good antibody response in children with lupus, as in control children. The response was not affected by the use of immunosuppressive therapy. No increase in autoantibody production or disease flare was seen. Finally, in the fifth paper on the subject, my colleagues and I²⁰ showed that influenza vaccination in patients with SLE was safe, there was a significant increase in antibody responses, patients developed protective antibodies despite immunosuppressive therapy and disease activity, anti-DNA antibodies did not change after vaccination, and induction and/or increase of autoantibodies was not constant and was not clinically significant. To further evaluate the duration of vaccine-induced antibody, serum samples of 7 patients who had completed 12 months after vaccination were taken. Six out of 7 had protective titers for all 3 influenza antigens, and one more patient had protective titers to only 2 antigens.

HEPATITIS B VACCINE AND SLE

Over the past few years, autoimmune hazards of hepatitis B (HB) vaccination have been described in the literature. Whether autoimmune manifestations are consequence or coincidence after administration of viral vaccines remains controversial. A recent extensive literature review²¹ showed (1) biologic plausibility of a relationship between HB surface antigen and SLE was unlikely; (2) case reports or series of patients who developed lupus after vaccination were rare and not convincing regarding potential causality; and (3) there were neither controlled observational studies nor controlled clinical studies. Therefore, the decision to vaccinate a patient with an immunological disorder should rely, not on case reports, but on evidence based medicine.

CONCLUSION

The safety and immunogenicity of vaccine against pneumococcus and influenza virus, first reported in the late 1970s, have now been confirmed. There is no evidence of exacerbation of disease. Patients with SLE develop protective antibodies despite disease activity and immunosuppressive drugs. Interestingly, the humoral immune response to these vaccines

is antigen-specific and independent of the production of anti-DNA antibodies, and the induction of autoimmune phenomena is an uncommon occurrence.

Because the prevention of microbial infection, which is a leading cause of morbidity in patients with SLE, is very important, they should receive these vaccines even though antibody levels may be lower than those of healthy controls. Therefore, it seems prudent to continue to monitor antibody titers. I believe that the measurement of antibody levels should be once a year, and patients may need revaccination against pneumococcus earlier than the recommended 5 years.

ULISES MERCADO, MD, MSc, FACR,
Professor of Medicine,
Hospital General de Mexicali
and Universidad Autónoma de Baja California,
Mexicali, Mexico

Address reprint requests to Dr. U. Mercado, 337 First Street, MSC 20765, Calexico, CA 92231, USA. E-mail: ulisesmercado@uabc.mx

REFERENCES

1. Alarcón-Segovia D, Alarcón-Riquelme M. Etiopathogenesis of SLE: a tale of three troikas. In: Lahita RG, editor. Systemic lupus erythematosus. San Diego: Academic Press; 1999:55-65.
2. Williams GW, Steinberg AD, Reinertsen JL, et al. Influenza immunization in systemic lupus erythematosus: a double-blind trial. *Ann Intern Med* 1978;88:729-34.
3. Brodman R, Gilfillan R, Glass D, et al. Influenza vaccine response in systemic lupus erythematosus. *Ann Intern Med* 1978;88:735-40.
4. Louie JS, Nies KM, Shoji KT, et al. Clinical and antibody responses after influenza immunization in systemic lupus erythematosus. *Ann Intern Med* 1978;88:790-2.
5. Ristow SC, Douglas RG, Condemi JJ, et al. Influenza vaccination of patients with systemic lupus erythematosus. *Ann Intern Med* 1978;88:786-9.
6. Herron A, Dettleff G, Hixon B, et al. Influenza vaccination in patients with rheumatic diseases. *JAMA* 1979;242:53-6.
7. Klippel JH, Karsh J, Stahl NI, et al. A controlled study of pneumococcal polysaccharide vaccine in systemic lupus erythematosus. *Arthritis Rheum* 1979;22:1321-5.
8. Jarrett MP, Schiffman G, Barland P, et al. Impaired response to pneumococcal vaccine in systemic lupus erythematosus. *Arthritis Rheum* 1980;23:1287-93.
9. McDonald E, Jarret MP, Schiffman G, et al. Persistence of pneumococcal antibodies after immunization in patients with systemic lupus erythematosus. *J Rheumatol* 1984;11:306-8.
10. Lipnick RN, Karsh J, Stahl NI, et al. Pneumococcal immunization in patients with systemic lupus erythematosus treated with immunosuppressives. *J Rheumatol* 1985;12:1118-21.
11. Battafarano DF, Battafarano NJ, Larsen L, et al. Antigen-specific antibody responses in lupus patients following vaccination. *Arthritis Rheum* 1998;41:1828-34.
12. Mercado U. Antibody responses following vaccination in lupus patients. *Rev Invest Clin* 2003;55:93-4.
13. Tarjan P, Sipka S, Marodi L, et al. No short-term immunological effects of pneumococcal vaccination in patients with systemic lupus erythematosus. *Scand J Rheumatol* 2002;31:211-5.
14. Pisoni C, Sarano J, Benchetrit G, et al. Antipneumococcal vaccination in patient with systemic lupus erythematosus. *Medicina (B Aires)* 2003;63:388-92.
15. Elkayam O, Paran D, Caspi D, et al. Immunogenicity and safety of

- pneumococcal vaccination in patients with rheumatoid arthritis or systemic lupus erythematosus. *Clin Infect Dis* 2002;34:147-53.
16. Abu-Shakra M, Zalmanson S, Neumann L, et al. Influenza virus vaccination of patients with systemic lupus erythematosus: effects on disease activity. *J Rheumatol* 2000;27:1681-5.
 17. Abu-Shakra M, Press J, Varsano N, et al. Specific antibody response after influenza immunization in systemic lupus erythematosus. *J Rheumatol* 2002;29:2555-7.
 18. Abu-Shakra M, Press J, Sukenic S, Buskila D. Influenza virus vaccination of patients with SLE: effects on generation of autoantibodies. *Clin Rheumatol* 2002;21:369-72.
 19. Kanakoudi-Tsakalidou F, Trachana M, Pratsidou-Gertsi P, Tsitsami E, Kyriazopoulou-Dalaina V. Influenza vaccination in children with chronic rheumatic diseases and long-term immunosuppressive therapy. *Clin Exp Rheumatol* 2001;19:589-94.
 20. Mercado U, Acosta H, Avendaño L. Influenza vaccination of patients with systemic lupus erythematosus. *Rev Invest Clin* 2004;56:14-8.
 21. Hanslik T, Vaillant JN, Audrain L, et al. Systemic lupus erythematosus and risk of hepatitis B vaccination: from level of evidence to prescription. *Rev Med Interne* 2000;21:785-90.