Leading article: Immunisation of patients with rheumatoid arthritis and systemic lupus erythematosus

Rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) are autoimmune diseases characterised by B cell hyperactivity and production of autoantibodies of many different specificities. A number of defects in immunoregulation have been identified and suggested as possible underlying mechanisms for excessive autoantibody production. Study of the immune response to challenge with exogenous antigen, in the form of immunisation, may add to our understanding of immunological processes in these diseases. There are many clinical considerations pertinent to the question of immunisation of patients with RA and SLE. For example, lupus patients, and less frequently those with RA, may have lung disease and therefore be at particular risk during influenza epidemics. Immunosuppressive therapy, commonly prescribed in both conditions, could also impair the immune response to foreign antigens, thus emphasising the need for immunisation or rendering it ineffective. In addition, the diseases themselves may predispose to infection. It is also our clinical impression that flares of disease may follow intercurrent infection, and we are not alone in this view. Again, influenza is a major contender for such intercurrent infection, so particular emphasis will be laid on influenza immunisation in this article.

Clearly the most important questions regarding immunisation in patients with autoimmune disease are (a) is it safe? (b) is it effective?

Is it safe?

The normal constraints on immunisation apply. As most vaccines are prepared on egg, patients with egg allergy are excluded, and caution should be exercised in the presence of other atopy. A report of six cases of Guillain-Barré syndrome after influenza vaccination in normal volunteers in America gave cause for concern, but no further cases have been reported subsequently. Extensive evaluation of the safety of influenza vaccination in patients with SLE has been carried out, and a low rate of adverse effects observed. One patient with active lupus developed renal disease after vaccination, which may have been coincidental. In our own series of 28 patients with SLE and 10 with RA local and systemic reactions to influenza vaccination were less common than in normal controls (presumably the result of concurrent treatment with anti-inflammatory agents). No patient showed a flare in disease activity after vaccination, by clinical or laboratory parameters, and most made a satisfactory serum antibody response, even while receiving steroids or other immunosuppressive therapy.

Is it effective?

Serum antibody response to vaccination in patients with SLE has been variously reported as normal, subnormal, or supernormal according to different authors, and depending on the different antigen studied (Table 1).

Discrepancy between these reports may be accounted for to some extent by the different methods used—for example, Meiselas and associates found an increased response to brucella using antigen at five times the concentration of that used by Baum and Ziff, who found a decreased antibody response in patients with SLE. An alternative explanation could be different HLA status between patients and controls. Certain HLA types have been associated with immune responses

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Response</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>Pneumococcus</td>
<td>Normal</td>
<td>Croft et al. 1984</td>
</tr>
<tr>
<td>Pneumococcus</td>
<td>Reduced</td>
<td>McDonald et al. 1984</td>
</tr>
<tr>
<td>Tetanus toxoid</td>
<td>Normal</td>
<td>Sarkany. 1961</td>
</tr>
<tr>
<td>Brucella</td>
<td>Decreased</td>
<td>Baum and Ziff. 1969</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>(mainly IgM)</td>
<td></td>
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<tr>
<td>Shigella</td>
<td>Normal</td>
<td>Lec et al. 1960</td>
</tr>
<tr>
<td>Brucella</td>
<td>Increased</td>
<td>Meiselas et al. 1961</td>
</tr>
<tr>
<td>Rickettsial</td>
<td>Normal</td>
<td>Louie et al. 1978</td>
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<td>Brucella</td>
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<tr>
<td>Influenza</td>
<td>Absent</td>
<td>Ristow et al. 1978</td>
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<tr>
<td>Influenza</td>
<td>Reduced</td>
<td>Williams et al. 1978</td>
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Table 1  Serum response to antigenic challenge in patients with SLE


to rubella and streptococcal antigens. In the latter the HLA-A5 type correlates with the ability to mount an in vitro antibody response to streptococcal antigen over a range of antigen concentration. The predominance of HLA-DR4 in RA and of HLA-DR2 and DR3 in some populations with SLE may explain heterogeneity among patients as well as the disparity in reported findings. Finally, the effect of prostaglandin inhibitors may be important. Steroids and immunosuppressive therapy may have been withdrawn during the study period, but non-steroidal anti-inflammatory drugs could still have altered the immune response.

Some workers have found impaired in vitro antibody responses to restimulation of peripheral blood mononuclear cells (PBMs) with influenza antigen after vaccination in patients with SLE, despite a ‘normal’ serum antibody response of a greater than fourfold rise in titre. One possible explanation for this would be an altered recirculation pattern of antibody producing cells in SLE, with sequestration in the lymphoid tissue, as demonstrated for varicella in patients with Hodgkin’s disease. Our own study has confirmed an impaired in vitro response in a group (9/28) of patients with SLE (although others had normal responses). In this group of in vitro non-responders lymph node lymphocytes were shown to make anti-influenza antibody in vitro (unpublished data). Serum responses were lower in the in vitro non-responder group (p=0.003), however, (even though they represented a greater than fourfold rise in antibody titre), indicating a more generalised depression of immune response in these patients.

Depression of the immune response could merely reflect the immunosuppressive drugs that many of these patients were taking, but there was no correlation with immunosuppressive therapy in our series or other series. An alternative explanation could be spontaneous polyclonal antibody production in these patients, rendering PBMs resistant to further stimulation. Spontaneous immunoglobulin synthesis by PBMs from patients with SLE in short term culture was demonstrated by Jasin and Ziff, suggesting increased numbers of highly differentiated antibody producing cells in the peripheral circulation. Dar and her colleagues have recently reported spontaneous production of antibodies to a variety of self and environmental antigens in such short term cultures of PBMs from lupus patients. Despite this spontaneous antibody production, pokeweed mitogen stimulation of immunoglobulin synthesis by PBMs is decreased in patients with active SLE and returns to normal when the disease becomes inactive. It is suggested that excessive activation of B cells renders them refractive to further stimulation. It is possible that the same mechanism could account for the lack of in vitro response after influenza vaccination. In this case one would expect a correlation with disease activity, which was not seen in our series. Non-responders had generally higher serum anti-DNA levels, but there was no evidence of autoantibody production at the expense of anti-influenza antibody, in response to vaccination, either in vivo or in vitro. Nor has this been seen in any other series of lupus patients, though patients with RA are shown to develop increased titres of rheumatoid factor (latex) corresponding to the specific antibody response to brucella and rickettsial vaccines.

In addition to evidence for a quantitative reduction in the immune response to specific antigen challenge in these patients, there is also evidence for qualitative changes. Differences in affinity and IgG subclass of antibodies produced after immunisation with tetanus toxoid have been demonstrated in patients with RA and SLE. Patients with RA failed to show affinity maturation, though they produced similar amounts of antibody to the controls. Antitetanus toxoid antibodies were predominantly IgG1 and IgG4 in the control group, but in RA and SLE there was either a restricted IgG1 response or a more general response in all the IgG subclasses, presumably reflecting the underlying immunoregulatory disorders in these patients.

Conclusions

1. Immunisation is probably safe in SLE and RA. There is no evidence that it is followed by flares in disease activity.
2. Even in patients receiving moderately large doses of immunosuppressive drugs most patients with RA or SLE make immune responses which are not quantitatively so different from those of normal controls.
3. It is suggested, however, that there may be qualitative differences in the antibody produced, which may mean that the protection afforded these patients by vaccination may be less complete than in normal individuals.

References


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