Vaccination in Patients with Chronic Rheumatic or Autoimmune Diseases

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Patients who have chronic rheumatic or autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, or vasculitides, show a risk of infection that is at least 2-fold greater than that for healthy individuals. This increased risk is not only a result of the aberrant immunologic reaction itself but also can be attributed to the immunosuppressive therapy required to control the activity of the underlying disease and the associated organ complications. Vaccination is an option for a substantial number of these infections. In this context, pneumococcal and influenza vaccines are the best evaluated and are recommended by standard vaccination guidelines. Some studies have found mildly impaired immune responses to vaccines among patients receiving long-term immunosuppressive therapy, but postvaccination antibody titers are usually sufficient to provide protection for the majority of immunized individuals. The accumulated data on the safety and effectiveness of vaccines warrant immunization with the majority of vaccines for patients with chronic autoimmune or rheumatic diseases, especially vaccination against influenza and pneumococci. Vaccination protocols for this population should be better implemented in daily clinical practice.

RISK OF INFECTION IN PATIENTS RECEIVING LONG-TERM IMMUNOSUPPRESSIVE THERAPY

In past years, substantial progress has been made in the treatment of chronic rheumatic and autoimmune diseases. Corticosteroids, azathioprine, and low-dose weekly methotrexate are widely used for these indications and are appropriate for most patients. Patients refractory to these conventional regimens can now be given effective treatment with the newer, “biological” agents, including TNF-α antagonists, rituximab (an anti-CD20 monoclonal antibody), and abatacept (a recombinant costimulatory inhibitory molecule). Without questioning the usefulness and effectiveness of immunosuppressive treatment for patients with chronic rheumatic or autoimmune diseases, it must be kept in mind that the manipulation of the immune system that is inherent to these therapies may increase the risk of infection for the patients. Recent analyses have estimated an incidence of severe infections in these patients that is ~2-fold greater than that in the general population.

Bone and joints, skin, soft tissues, and the respiratory tract are sites frequently involved in infectious processes in patients who have rheumatoid arthritis [1]. In patients with chronic inflammatory rheumatic or autoimmune diseases without arthritis, infections of the respiratory tract are the most common. The risk of infection is also dependent on the degree of immunosuppression associated with disease-modifying antirheumatic drugs (DMARDs), most of which also have cytostatic effects [2–4]. Corticosteroids play an important role in this context because they are often used together with DMARDs and appear to increase cytotoxic effects, the degree of immunodeficiency, and the risk of infection in a dose-dependent manner [2, 3]. The “biological” DMARDs—namely, TNF antagonists, rituximab, or abatacept—are often used together with traditional DMARDs for patients with highly active autoimmune disease. These new agents amplify the immunosuppressive effects of traditional DMARDs by additional lymphocyte toxicity and inhibition of important cytokine and noncytokine activation pathways. Data from a large retrospective US study [5] and a German national database [6] demonstrated an increased infection rate among patients during treatment with TNF antagonists, compared with during treatment with tra-
ditional DMARDs. The use of TNF antagonists has also been identified as a risk factor for tuberculosis and other infections associated with a dysregulated Th1 response and also for mortality in patients with pneumococcal infections.

Some investigations have identified a treatment-related lymphopenia (<600 lymphocytes/μL), rather than the individual therapeutic regimen, as the most prominent risk factor for infection. Absolute CD4+ T cell counts in patients receiving aggressive, long-term immunosuppressive therapy have been found to be decreased to an extent similar to that in patients with advanced HIV infection. Such patients have the highest risk of infection, not only for typical opportunistic infections, such as tuberculosis or Pneumocystis pneumonia, but also for infections that are common in the general population [3]. Common infections, in particular, are responsible for the majority of infectious episodes in patients receiving long-term immunosuppressive therapy [7].

Vaccines are available for a number of these infections and are a window of opportunity for prophylaxis. However, given the treatment-associated immune defects described above, several questions need to be addressed with regard to the immunogenicity, efficacy, and safety of standard vaccine preparations for these patients. In this review, the current evidence on these topics is summarized.

PNEUMOCOCCAL VACCINES

Two pneumococcal vaccines are commercially available. The polysaccharide vaccine contains antigens of the 23 most-common pneumococcal strains that together cause ~88% of all pneumococcal infections. Vaccination is recommended for patients aged >65 years, for patients with asplenia, and for individuals with chronic diseases, regardless of age. In addition, a heptavalent conjugate vaccine has been licensed recently for children aged <5 years, who generally show a poor response to polysaccharide antigens.

Immunogenicity of pneumococcal vaccine in patients with chronic rheumatic or autoimmune diseases. Since the 1980s, immune responses to the polysaccharide vaccine have been tested in several small studies [8–13] and have been reviewed by Elkayam et al. [14]. In general, the average antibody titers at 1 month to 1 year after vaccination were equal or slightly reduced in patients receiving conventional immunosuppressive agents and/or corticosteroids, compared with those in control individuals. The most detailed investigation by Elkayam et al. [13] found similar geometric mean postvaccination titers among the patients regardless of treatment, but 33% of the patients with rheumatoid arthritis and 21% of the patients with systemic lupus erythematosus (SLE) showed only minimal and likely nonprotective responses to the vaccine. The influence of prednisolone therapy on vaccine responses has not been evaluated in patients with chronic rheumatic or autoimmune diseases. In patients with chronic obstructive pulmonary disease or asthma, however, corticosteroid therapy did not compromise the immune response to the pneumococcal polysaccharide vaccine [15]. De Roux et al. [15] detected a 16%–21% rate of nonresponse among patients and healthy control individuals; other studies did not find nonresponders [16]. There are no studies of the effects of cyclosporine in patients with autoimmune diseases and chronic immunosuppression; however, in patients receiving cyclosporine therapy after heart transplantation, no impaired immune responses to the pneumococcal polysaccharide vaccine were observed [17].

The introduction of the biological DMARDs for treatment of rheumatic diseases has prompted several investigations with respect to the effects of these agents on immune responses after immunization with the pneumococcal vaccine. Elkayam et al. [18] studied antibody responses at 1 month after pneumococcal vaccination in 16 patients receiving treatment with methotrexate and etanercept or infliximab compared with those in 17 matched patients receiving methotrexate monotherapy. The patients receiving TNF antagonists showed a trend toward lower antibody responses for most of the antigens tested, and 31% of these patients were poor responders, compared with 18% of those receiving methotrexate monotherapy [18]. Kapetanovic et al. [19] compared responses to the 23F and 6B pneumococcal antigens in patients with rheumatoid arthritis receiving methotrexate alone with those in patients receiving combination therapy with TNF antagonists. Postvaccination antibody levels in patients given treatment with a TNF antagonist alone or a combination of a TNF antagonist and a DMARD other than methotrexate were similar to those in healthy control individuals but were significantly higher than those in patients receiving only methotrexate. More than 2-fold increases in titers against the 2 antigens were seen in ~50% of patients receiving monotherapy with a TNF antagonist and in 40% of healthy control individuals but in only 15% of patients receiving methotrexate monotherapy [19]. Immune responses to 5 of the 23 antigens of the polysaccharide vaccine were investigated by Mease et al. [20] in 184 patients with psoriatic arthritis receiving therapy with methotrexate alone or in combination with etanercept. Approximately 20% of the patients in each group did not show a ≥2-fold antibody titer increase against any of the antigens. Logistic regression analysis identified methotrexate therapy and older age but not treatment with etanercept as independent factors for attenuated immune responses [20]. On the other hand, Visvanathan et al. [21] failed to show differences in antibody responses between patients with rheumatoid arthritis receiving methotrexate alone and patients receiving methotrexate in combination with infliximab but they noted reduced responses in those patients compared with healthy control individuals. In that study, 80%–85% of the patients responded to at least 1 pneumococcal antigen, but only 20%–
25% of patients responded to ≥6 antigens. Kaine et al. [22] investigated responses to pneumococcal vaccination in patients with rheumatoid arthritis receiving conventional DMARDs and adalimumab or placebo. That study found similar response rates of 37.4% of patients for the group receiving treatment and 40.4% for the placebo group, as well as protective antibody titers in 85.9% and 81.7% of patients, respectively [22].

Abatacept and rituximab have been licensed recently for the treatment of rheumatoid arthritis, and detailed studies of immune responses to pneumococcal vaccines in patients receiving treatment with these agents are not yet available. Rituximab results in a long-lasting depletion of B cells. A decreased or blunted antibody response to vaccines, therefore, should be expected and has been demonstrated in patients with lymphoma who received treatment with rituximab. Of note, plasma cells appear to be less affected. Preliminary data did not show a decrease in preexisting antibody titers against tetanus, influenza, or pneumococcal antigens in patients receiving rituximab therapy during a 24-week period [23], but studies evaluating longer periods are not currently available. Abatacept acts by inhibiting costimulatory pathways, which are essential for generation of an immune response to protein and peptide antigens. Decreased responses to such antigens, therefore, can be predicted, whereas T cell–independent responses to polysaccharide (e.g., pneumococcal) antigens should not be affected. However, a study involving volunteers revealed decreased immune responses after tetanus and pneumococcal vaccination [24]. Similar effects can also be expected for patients with chronic rheumatic and autoimmune diseases, but data are not available.

Important issues are how long the protective titers after pneumococcal vaccination last for patients receiving immunosuppressive therapy and when such patients should be revaccinated. McDonald et al. [25] followed up patients with SLE for up to 3 years after vaccination and found decreasing titers that were considered to be no longer protective in 8 of the 19 patients tested. However, similar decreases in titers were seen in healthy persons [26]. The matter of revaccination, a topic of dispute even for healthy populations, is still unclear for immunocompromised patients. The pneumococcal conjugate vaccine has been licensed only for children to date. No studies are available on the immune response to this vaccine in patients receiving immunosuppressive therapy for rheumatic or autoimmune diseases. However, the conjugate pneumococcal vaccine has been shown to induce protective antibody titers in children with generally impaired immune responses at 6–9 months after bone marrow transplantation [27].

**Effectiveness of pneumococcal vaccines in patients with chronic rheumatic or autoimmune diseases.** No data are available on the effectiveness of pneumococcal vaccination in patients with autoimmune diseases. In other populations, however, vaccination against pneumococci has proved to be effective. In children aged <5 years, use of the pneumococcal conjugate vaccine has been shown to decrease significantly the rate of invasive pneumococcal infection [28–30]. The effect was most pronounced for infections caused by the serogroups covered by the heptavalent vaccine. A significant protective effect of pneumococcal vaccination has also been shown recently for elderly people [31].

**INFLUENZA VACCINES**

Annual vaccination against influenza is generally recommended for persons aged >50 years (>60 years in Europe), individuals with chronic diseases, and patients with impaired immune responses. Several studies have investigated the various aspects of influenza vaccination for patients receiving DMARD therapy. All these investigations were performed with the inactivated influenza vaccine, not with the live, intranasally administered attenuated vaccine (Flumist; MedImmune).

**Immunogenicity of influenza vaccine in patients receiving long-term immunosuppressive therapy.** Abu-Shakra et al. [32] studied titers after influenza vaccination in 24 patients with SLE and 20 healthy control individuals. Six weeks after vaccination, the patients with SLE generated immune responses against a mean of 1.5 of the 3 influenza vaccine antigens, and 75% of patients responded to at least 1 antigen. Lower immune responses were found in patients aged ≥50 years, in those receiving prednisone treatment at a daily dosage of ≥10 mg, and in those receiving treatment with azathioprine but not in those receiving methotrexate treatment [32]. Holvast et al. [33] analyzed 56 patients with SLE receiving treatment with various DMARDs and found significantly fewer seroconversions or at least 4-fold increases in titers after influenza vaccination (39%–43%), compared with those in healthy control individuals (71%–94%), with rates depending on the antigen. Treatment with azathioprine was found to be associated with reduced vaccine response [33]. In contrast, Chalmers et al. [34], Fomin et al. [35], and Del Porto et al. [36], who respectively investigated 126, 82, and 48 patients with rheumatoid arthritis or SLE receiving various immunosuppressive regimens, did not identify any influence of DMARD treatment, corticosteroid treatment, or disease activity on the immune responses after influenza vaccination, compared with those in healthy control individuals.

TNF antagonists appear to have little impact on the response to influenza vaccines. Kaine et al. [22] found rates of protective antibodies in patients with rheumatoid arthritis receiving adalimumab similar to those in patients receiving placebo and found similar response rates in those who did not already have protective antibodies before vaccination. Protective antibody titers were found after vaccination in 98% of patients receiving adalimumab and 94.5% of patients receiving placebo, respectively [22]. Kapetanovic et al. [37] investigated responses to...
influenza vaccination in 149 patients with rheumatoid arthritis receiving methotrexate alone or in combination with TNF antagonists. Patients with rheumatoid arthritis given treatment with methotrexate without TNF antagonists had significantly better serological responses to influenza vaccination than did those receiving TNF antagonists alone or in combination with methotrexate and/or other DMARDs. Nevertheless, the majority of patients developed protective antibody levels after vaccination: from 52% against H1N1 to 94% against B1, depending on the antigen [37]. Similarly, Gelinck et al. [38] found, in a large group of patients with various autoimmune diseases, significantly lower geometric mean anti-influenza titers after influenza vaccination among patients receiving TNF antagonists. Approximately 80% of patients receiving TNF antagonists developed protective antibody titers, which was slightly but not significantly lower than the rates for patients receiving conventional DMARDs (82%–93%) and for healthy control individuals (89%–94%) [38]. Preliminary data also presented by Gelinck et al. [39] indicate that treatment with rituximab significantly diminished the immune responses to influenza vaccination.

**Effectiveness of influenza vaccine in patients with chronic rheumatic or autoimmune diseases.** Two small studies found lower infection rates after influenza vaccination in patients with SLE or rheumatoid arthritis and in children with rheumatic diseases [40, 41]. A well-structured investigation that studied patients after bone marrow transplantation showed a significant reduction of influenza cases among vaccinated individuals and estimated an efficacy of 80% for the vaccine. In other patient populations, however, the beneficial effects of influenza vaccination have been clearly demonstrated. Effectiveness for elderly people has been evaluated and validated in several meta-analyses. The best evidence comes from a recently published, 10-year, longitudinal study involving 713,872 person-seasons of observation, which found a highly significant 48% reduction in mortality and a 27% reduction in hospital admissions throughout the observation period.

**IMMUNOGENICITY OF THE HEPATITIS B VACCINE**

Vaccination against hepatitis B virus is generally recommended by numerous national immunization guidelines. Immunity against hepatitis B virus is especially relevant for patients beginning immunosuppressive regimens—for example, treatment for malignant diseases or long-term immunosuppressive therapy—because fulminant reactivation of latent chronic hepatitis B virus may develop under such conditions as a life-threatening complication. Safety and efficacy of vaccination against hepatitis B virus in patients with rheumatoid arthritis have been evaluated by Elkayam et al. [42]. Only 15 of 22 patients responded to a standard vaccination protocol, as shown by development of an antibody level for anti-hepatitis B surface antigen of ≥10 IU/L after 7 months [42].

**IMMUNOGENICITY AND SAFETY OF THE VARICELLA ZOSTER VACCINE**

Varicella zoster vaccine has been licensed recently in the United States and in some European countries for elderly patients at risk for herpes zoster virus infection, to prevent postherpetic neuralgia [43]. Patients receiving long-term immunosuppressive therapy are also at increased risk for developing herpes zoster. In patients with systemic lupus erythematosus, herpes zoster has been identified as one of the most common infections associated with immunosuppression [7, 44, 45]. Use of a live attenuated vaccine in immunocompromised patients is of potential concern, and the vaccine has not been approved for use in such patient groups. However, the risks associated with live vaccines presumably depend on the degree of immunodeficiency. As an example, varicella zoster vaccine has proved to be immunogenic, well tolerated, and effective in prevention of herpes zoster episodes in children with HIV infection and after renal or bone marrow transplantation. An inactivated varicella zoster vaccine has been evaluated in patients planning to undergo autologous stem-cell transplantation. It was found to be immunogenic and effective. Vaccine recipients showed significantly increased specific T cell responses and significantly fewer clinical herpes zoster episodes in a 12-month period after transplantation than did patients who did not receive the vaccine [46].

**SAFETY OF THE MEASLES, MUMPS, AND RUBELLA VACCINE**

Immunization with 2 doses of the measles, mumps, and rubella vaccine is recommended for children aged >1 year. Because the vaccine contains live attenuated viruses, the same theoretical concerns as for the varicella zoster vaccine apply, which potentially precludes its use for immunocompromised individuals. However, in a retrospective study involving 314 vaccinated and nonvaccinated children with juvenile idiopathic arthritis, Heijstek et al. [47] were unable to demonstrate adverse effects or changes in disease activity, regardless of methotrexate treatment. Antibody titers were not measured in that study. Similar safety experience has been reported for the vaccine in children with DiGeorge syndrome, in children after bone-marrow or solid-organ transplantation, and in HIV-positive children without severe immune defects. Protective titers can be expected in 70%–90% of vaccine recipients. However, in HIV-positive children with severe immune defects, cases of measles, mumps, and rubella after vaccination have been observed.
VACCINE SAFETY IN PATIENTS WITH CHRONIC RHEUMATIC OR AUTOIMMUNE DISEASES

Numerous case reports indicate that vaccination may trigger or worsen autoimmune and rheumatic diseases, which is suggested by a timely relation between vaccination and disease exacerbation. Proinflammatory cytokines released during the immune response to vaccine antigens or mechanisms of molecular mimicry may be responsible for the initiation of a hitherto hidden rheumatic or autoimmune inflammatory process. The most frequently reported autoimmune manifestations after the various vaccinations were arthritis, vasculitis, encephalitis, neuropathy, and multiple sclerosis for the hepatitis B vaccine; acute reactive or chronic arthritis for the measles, mumps, and rubella vaccine; Guillain-Barré syndrome for the influenza vaccine; and various neurological disorders for the varicella vaccine [48]. Even these “frequent” associations involve a very small proportion of vaccine recipients. There is still controversy about whether hepatitis B vaccination is associated with increased risk of development of demyelinating CNS disorders. Early reports that indicated an increased risk [49] were not confirmed by more-recent analyses [50]. Furthermore, whenever controlled, prospective vaccine-safety studies involving patients with autoimmune diseases were performed, no evidence of the exacerbation of existing autoimmune diseases or of the induction of new rheumatic or autoimmune processes was found [8, 14, 33, 34, 36]. However, the relatively small numbers of patients included in these studies may have precluded the detection of rare events.

VACCINE ACCEPTANCE AMONG PATIENTS WITH RHEUMATIC DISEASES

Small surveys among patients with rheumatic diseases revealed a moderate-to-good acceptance of influenza vaccination (50%–80%) and a <50% acceptance of the pneumococcal vaccine [51, 52]. However, it is unclear whether these small surveys are representative. In many regions, influenza and pneumococcal vaccine coverage may not be stronger in chronically immunosuppressed patients than in the general population. Of note, there are also considerable differences in the general population in different countries. Awareness and coverage of influenza vaccine are usually better in the United States [53] than in Europe [54], with wide variations within countries. However, even in high-risk populations, 30%–40% coverage rates are rarely exceeded.

SUMMARY AND RECOMMENDATIONS FOR PATIENTS RECEIVING LONG-TERM IMMUNOSUPPRESSIVE THERAPY FOR RHEUMATIC AND AUTOIMMUNE DISEASES

Only relatively small studies have investigated the influence of DMARDs on the immunogenicity of pneumococcal and influenza vaccine in patients with chronic rheumatic and autoimmune diseases, and these studies do not result in a uniform picture. Conventional DMARDs, such as methotrexate or azathioprine, appear to have only modest impact on postvaccination titers. In general, 20%—and, in some studies, up to 50%—of the patients do not develop protective antibody levels. Among the newer, “biological” DMARDs, the TNF antagonists also appear to only slightly diminish antibody responses to vaccines. In contrast, the preliminary data available thus far for rituximab and abatacept suggest that these agents may have the potential to blunt immune responses, and more studies of these agents are urgently needed.

Although several case reports suggested associations between vaccinations and induction or exacerbation of autoimmune reactions, they could not be confirmed in prospective investigations or in carefully controlled case-control studies. Thus, the risk-to-benefit ratio of vaccination can be considered favorable for patients with stable rheumatic or autoimmune diseases, especially with regard to the pneumococcal and influenza vaccines.

Several problems still need to be clarified. It is essentially unclear how long vaccine-induced immunity lasts in patients receiving long-term immunosuppressive therapy. Similarly, no data are available as to whether vaccinations actually protect patients with chronic rheumatic or autoimmune diseases against the respective infections, although we have reason to assume that the benefit may be similar to that achieved in the general population. However, increased attention should be paid to the hepatitis B immune status before initiation of immunosuppressive therapy. Immune response to this vaccine is known to be attenuated in immunocompromised patients, and this appears to be the case also in patients with chronic autoimmune disorders. Future research should focus on vaccines for prevention of herpes zoster, specifically in patients receiving long-term immunosuppressive therapy. In summary, the available evidence is sufficient to encourage vaccinations for patients who receive immunosuppressive therapy with DMARDs and for chronically immunocompromised patients.

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