Patients with rheumatoid arthritis and other chronic rheumatic diseases are at approximately doubled risk of infection compared with the normal population [1]. This may be in part due to still ill-defined immunoregulatory abnormalities associated with rheumatic diseases, but is certainly in large part secondary to the immunosuppressive therapy administered to these patients in the best interest of their joints, with proven efficacy in delaying joint destruction. The effect of disease-modifying therapies on the immune system, however, may be quite dramatic, especially if aggressive protocols such as Fauci’s are administered, and they may lead to opportunistic infections otherwise only seen in patients with advanced HIV infection [2]. Inhibition of lymphocyte proliferation by DMARDs leading to lymphocytopenia is one of the key underlying mechanisms of this phenomenon, and lymphocyte counts less than 500/μl or CD4 counts less than 250/μl—quite comparable to patients with HIV-infection—have been found associated with an increased risk of infection [1, 3]. The respiratory tract is the organ system most commonly affected in patients with rheumatic diseases under chronic immunosuppressive disease-modifying therapy, similar to patients with other immunocompromising conditions or therapies [1, 3]. Fortunately, typical opportunistic pathogens such as Pneumocystis jiroveci (carinii) are rare in our patients, and classic bacterial infections of the respiratory tract are far more common [1, 3].

What can be done to overcome these problems? Antibiotic prophylaxis is a theoretical option and has been tried, but is complicated by many side-effects and may not be an effective long-term approach in the light of increasing bacterial resistance worldwide (while possibly contributing to it). There is certainly broad agreement that patients with rheumatic diseases fulfil each of the criteria of patients with a chronic condition, and for such patients pneumococcal and influenza vaccinations are advocated in most national immunization guidelines, e.g. the Centers for Disease Control and Prevention’s recommended adult immunization schedule [4], or the German STIKO recommendations [5].

Two questions arise in the context of these thoughts. (i) May the same mechanism as that which puts our patients at increased risk of infection also reduce their response to vaccines? (ii) Does the activation of the immune system, when responding to the immunizing antigen, induce a flare of the underlying rheumatic disease, e.g. due to proinflammatory cytokines? Unfortunately, for both vaccinations no large-scale trials addressing these questions have so far been performed in patients with rheumatic diseases.

In this issue of Rheumatology, Kapetanovic et al. present their results of monitoring the immune response of patients with rheumatoid arthritis to pneumococcal immunization with the standard 23-valent polysaccharide vaccine [6]. They were able to show that the immune responses to pneumococcal antigens were impaired by methotrexate (MTX) treatment but not by anti-TNF agents. This may be explained by the different modes of action of these two DMARDs: MTX inhibits cell proliferation unselectively, while anti-TNF agents block TNF specifically, and TNF does not play a very important role in the induction of an antibody immune response. The findings of Kapetanovic et al. are in line with those of Mease et al., who investigated the response to the 23-valent pneumococcal vaccine in patients with psoriatic arthritis under treatment with etanercept and/or MTX and found lower titres against the vaccine antigens only in association with MTX treatment [7]. However, it needs to be stressed that a substantial proportion of the patients receiving MTX in both investigations have shown sufficient induction of antibodies.

Response to pneumococcal vaccination has also been studied in other immunocompromised patient groups, such as patients on chronic corticosteroid therapy for chronic obstructive pulmonary disease [8], among whom the antibody responses were not found to be compromised by corticosteroid therapy; cancer patients [9], who showed a weaker response compared with healthy controls; patients on chronic stress [10], who did show impaired responses; and in heart transplant recipients under a cyclosporin-based regimen, who showed responses comparable to those of healthy adults [11]. Of note, antibody titres tend to decline more rapidly in immunocompromised patients, who may require booster vaccinations more frequently [12].

Whether immunization actually prevents disease is much more difficult to prove than whether there is an immune response to vaccine antigens. In this context no specific data for patients with rheumatic diseases exist. Meta-analyses have suggested that pneumococcal vaccination is uniformly effective in preventing infections, and is also cost-effective overall [13, 14]. More recently, a large study has questioned the preventive effects in elderly persons, except for bacteraemia [15].

Influenza vaccination is also recommended for immunocompromised patients, as influenza can take a more severe course in such patients. In contrast to the pneumococcal vaccine, influenza vaccination must be given every year. As the antigens in the two vaccines are different (polysaccharides in the pneumococcal vaccine and viral proteins in the influenza vaccine), the immune responses may also differ. Two studies in patients with rheumatoid arthritis found antibody responses following influenza immunization to be similar to those in normal controls [16, 17], but responses in patients after heart transplantation were somewhat impaired [11]. Despite these limitations, there is profound evidence that influenza vaccination is highly effective in preventing morbidity and mortality in elderly people and in patients with chronic conditions [18]. It may even be cost-effective for normal working adults [19].

Occasional case reports described an exacerbation or precipitation of rheumatic disease in close time association with immunnizations. A detailed review is beyond the scope of this editorial; however, in controlled trials such concerns could not be confirmed [12].

Thus, it can be concluded that the standard 23-valent pneumococcal and the yearly influenza vaccines should be safe and sufficiently antigenic to induce an antibody response in patients with rheumatic diseases, even if some patients will not respond to all antigens in the vaccine preparations and the titres may be somewhat lower and less persistent than in healthy adults. More research needs to be done to optimize immunization protocols for immunosuppressed patients, e.g. by giving booster doses more frequently. It has to be mentioned, though, that even healthy persons do show substantial interindividual variation in titre and the number of antibody responses to vaccines [20].

So, vaccinate your immunosuppressed patients! Especially now, in the winter season, this take-home message must be
regarded as most appropriate. Currently, vaccination rates are 20–35% at best. It is up to us doctors to motivate our patients to receive adequate immunization. We have to make immunization part of the treatment plans for our patients, otherwise these vaccination rates will not increase and our patients will be left unprotected [21].

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