Pneumococcal Vaccination Strategies in the Real World of Chronically Ill Patients

Throughout the world vaccination strategies are widely applied because they are cheap and cost-effective. The World Health Organization (WHO) provides recommendations for routine immunizations[1]. These recommendations are primarily based on vaccine studies performed in healthy children or elderly persons without significant comorbidity. For instance, the CAPITA study (Community-Acquired Pneumonia Immunization Trial in Adults) on about 85,000 adults aged 65 years and older is seen as a landmark study, demonstrating that a pneumococcal conjugate vaccine prevents a significant proportion of pneumococcal community-acquired pneumonia in adults[2]. The study is of considerable public health significance. However, in the real world the pneumococcal vaccine is not administered to the entire healthy elderly population. In contrast, this and other vaccines are given especially to protect chronically ill patients. In the above-mentioned CAPITA study, adults were excluded if they resided in nursing homes, had significant comorbidity that could result in an immune-suppressed state, or had medications that could affect the immune response. As a result, the decision to vaccinate these chronically ill patients is left to the discretion of the doctor. In the rheumatology field this has led to numerous investigator-initiated studies in adult and pediatric rheumatic diseases. Several reviews were published with immunization recommendations for adults and children with rheumatic conditions[3,4,5]. These immunization recommendations take into account the 2 main issues that play a role in patients with rheumatic diseases using immunosuppressive drugs: the safety and the efficacy of vaccines.

Regarding safety, the product labels of most vaccines state that concomitant use of immunosuppressive drugs such as methotrexate (MTX) or biological disease-modifying antirheumatic drugs (DMARD) are a contraindication for vaccination. In particular, live-attenuated vaccines (measles, mumps, rubella, yellow fever, varicella zoster) carry the risk of enhanced replication of the attenuated pathogen in immunocompromised patients, thereby causing complica-tions such as vaccine-associated measles, encephalitis, or pneumonia.

Patients and doctors need to balance the risk of vaccination-induced complications against the (increasing) risk of natural exposure to these microorganisms in the community. This is more easily said than done because such risk-benefit analyses will always be hampered by scarcity of data. It is simply impossible to perform sufficiently powered studies to assess the risk of vaccine-induced infectious complications or the infectious risks of withholding these vaccines in patients using MTX and biologicals. Reassuring studies including small numbers of patients with juvenile idiopathic arthritis (JIA) using biologicals showed that the live-attenuated vaccine for measles, mumps, and rubella did not induce severe adverse events[6,7]. Unfortunately, to date no clinical or laboratory measurements allow accurate assessment of the immune status to identify patients at increased risk of infectious complications induced by live-attenuated vaccines. Future vaccine studies should focus on the safety of live-attenuated vaccines in patients treated with biologics, and on the identification of factors associated with vaccine-induced adverse events.

Regarding efficacy, infection rates after vaccination are rarely analyzed as the primary endpoint of vaccination studies. To study infection rates as primary outcome, longterm followup and large sample sizes are required. Because of these difficulties, most studies assess vaccine-induced immune responses as correlates and/or surrogates of protection against infections. The majority of studies on pneumococcal vaccination in patients with rheumatic diseases also study (short-term) humoral and cellular immune responses as endpoints for vaccine efficacy. Children and elderly persons with rheumatic diseases have an increased risk of complicated pneumococcal infections. The guidelines mentioned above thus strongly recommend pneumococcal vaccination in patients with rheumatic conditions[3,4]. Pneumococcal polysaccharide vaccination (PPSV) in patients with rheumatoid arthritis (RA), systemic lupus

erythematosus (SLE), spondyloarthropathy, and systemic sclerosis induces an adequate to slightly reduced humoral response[3]. Unexpectedly, MTX reduces humoral response following PPSV in patients with RA and SLE[8]. In patients with JIA, adding anti-tumor necrosis factor (anti-TNF) therapy to MTX does not seem to have an additional suppressive effect on immunogenicity of the 23-valent PPSV compared to MTX alone[9], whereas anti-TNF reduced the immunogenicity of the 7-valent conjugate pneumococcal vaccine in children with JIA[10]. Thus, both MTX and anti-TNF treatment may reduce the short-term immunogenicity of pneumococcal vaccines. To ensure longterm protection against vaccine-preventable infections, protective antibody levels should be persistent. However, most studies have limited followup periods, and data on persistence of protective antibody concentrations are limited. Therefore, regular assessment of antibody levels and subsequent administration of booster vaccines in case of waning antibody levels in these patients are important to ensure longterm protection.

The article of Broyde and colleagues in the current issue of *The Journal* is interesting because it promotes an active pneumococcal vaccination strategy and serological longterm followup in adults with autoimmune inflammatory conditions[11]. Their report is an elegant and simple study on the longterm immunogenicity of the 23-valent anti-pneumococcal polysaccharide vaccine (PPSV23)[11]. Included were 145 adults with autoimmune inflammatory conditions, mostly RA, who were treated with biologics (TNF-α receptor blockers or anti-interleukin 6 antibodies) or MTX. After inclusion, a serum sample was taken and demographic data were collected including medication history and vaccination status. Fifteen patients were excluded for lack of information on the pneumococcal vaccination date or availability of blood for serology. Serology was performed for the combination of all serotypes in the PPSV23 vaccine. An antipneumococcal antibody level of 35 mg/l or higher was taken as protective. To address the study aim of longterm vaccine protection, patients were analyzed in subgroups according to time since vaccination. Twenty-five percent of patients received their PPSV23 vaccination at least 5 years earlier. There was no statistically significant difference in antibody levels between more recently vaccinated patients and patients vaccinated at least 5 years ago. This study is important because it shows the persistence of protective antibody titers well after 5 years. Current guidelines state that revaccination against pneumococci after 5 years may be considered in immunocompromised patients because of waning immunity. Based on these data, it may not be necessary to revaccinate all patients. These data underscore the recommendation for monitoring serology for 5 years post-vaccination, followed by booster vaccination when antibody titers are nonprotective[3]. This recommendation applies not only to the pneumococcal vaccine: Indeed, our longterm DTP and meningococcal serotype C serology studies in children with JIA also show declining titers in a subset of patients, favoring periodic serological testing especially when under biological therapy[12,13].

The controls in this study were nonvaccinated rheumatology patients. The majority of patients in the control group were not vaccinated because of lack of awareness. The study nicely illustrates the importance of active vaccination strategies in nonvaccinated patient groups because routine serology testing in these patients detects nonprotective antibody levels in almost one-third (29.1%) of patients (vs 10% in the vaccinated group). Although these data also point out that 71% of unvaccinated rheumatic patients are protected, the 29% unprotected patients are at increased risk of complicated invasive pneumococcal infections.

The implications of this study are also of value for other chronic inflammatory conditions such as inflammatory bowel disease (IBD). Here also vaccination strategies must be developed. Vaccination response patterns in IBD seem to differ markedly from most rheumatic conditions[14]. Nguyen, *et al* also proposed routine monitoring of vaccine titers post-vaccination in patients with IBD[14].

The study by Broyde and colleagues[11] has several limitations: The duration of therapy with MTX was not determined. Often patients use MTX prior to biologics, as monotherapy. The extent to which immune competence is impaired depends on the type and dose of medication used, as well as the duration of therapy[15]. And owing to the retrospective nature of this study, no data were available on the adverse events of vaccination and its effect on preventing pneumococcal infections or hospitalizations. Thus one is left with pneumococcal serology as a surrogate marker of vaccine efficacy. Relevant events such as severe infections and hospitalizations should be documented as events of specific interest in large-scale registries.

The study by Broyde, *et al* underscores the importance of proactive vaccination strategies with longterm management, preferably guided by periodic serology testing, to ensure that in the real world of vaccinating chronically ill patients, these patients are indeed safely vaccinated and protected for the long term against invasive infections.

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