Commentary (Ljungman): Vaccinations Against Infectious Diseases in Hematopoietic Stem Cell Transplant Recipients

By Per Ljungman, MD, PhD

As increasing numbers of stem cell transplant recipients become long-term survivors, interest in understanding their long-term immune status also assumes greater urgency. One important strategy for protecting patients against certain infections is the use of vaccinations. Just a few years ago, there were no published recommendations regarding this issue. Since then, both the European Group for Blood and Marrow Transplantation (EBMT) and the Centers for Disease Control and Prevention (CDC) have published recommendations. Drs. Goldberg, Cicogna, Rowley, and Pecora critically review the CDC recommendations in a nicely written article and provide important background information.

Surrogate End Points

They characterize the current scientific literature on the subject as anecdotal reports, expert advice, summaries, and limited series of patients using surrogate end points, overall resulting in inadequate scientific information upon which to base recommendations. Although this is certainly true to some extent and makes the existing literature partly confusing, practical issues concerning these types of studies can be commented upon. The surrogate markers used to determine immunity and/or response to vaccination are measurements of antibody levels; ie, studies are not designed specifically to evaluate protection against infection. The problem is that, with the possible exception of influenza, the number of patients required to accurately analyze the protective efficacy of vaccination would make such studies completely unfeasible. Even in influenza, the study would have to be performed during a major outbreak to have enough power to show protective efficacy. Pneumococcal infections are quite common, but given the recent EBMT data showing an incidence of 2.0 and 8.6 cases per 1,000 transplants for early- and late-occurring invasive pneumococcal infections, respectively,[1] and the fact that recently performed studies of conjugated pneumococcal vaccine in healthy children have included thousands of patients, ongoing studies (in both the United States and Europe) of the 7-valent conjugate vaccine (Prevnar) will also include serologic response as a primary end point. For rare infections in stem cell transplant patients such as diphtheria and tetanus, it is inconceivable that protective efficacy studies could ever be performed. Thus, surrogate end point studies are likely to be the only ones upon which recommendations can be based in the future.

Safe Assumptions

That said, many published studies are small and poorly controlled, and clearly better studies can and should be performed. In addition, the great variability in transplant techniques and the rapid development of new techniques—such as the use of reduced-intensity conditioning before transplantation and the use of alternative sources of stem cells other than bone marrow or peripheral blood—make this field even more confusing. Nevertheless, a few aspects of vaccination can be stated with some confidence despite the current
status of the published literature. Non-live vaccines are safe and do not induce more side effects in stem cell recipients than in healthy individuals. Moreover, the timing and dose schedule of vaccinations are critical to the results.

**Infectious Complications**

The authors clearly present the current status of the literature regarding pneumococcal vaccination. The main problem with the polysaccharide vaccine is the poor response rate, whereas the main problem with the 7-valent conjugate vaccine may be that it covers fewer pneumococcal subtypes than the 23-valent vaccine. Therefore, it will be critical in all future studies of the new vaccine, with or without the addition of a dose of the 23-valent vaccine, to follow patients for a long time poststudy to determine the risk for breakthroughs of serotypes not included in the vaccine. The authors state that severe, lifethreatening influenza infections may occur during the early aplastic phase of transplantation. Although this is certainly true, it must be emphasized that fatal infections can also occur several years after stem cell transplant.[2] Moreover, there seems to be no major difference in the risk for fatal influenza infections between autologous and allogeneic recipients. This is important because it supports the concept that stem cell transplant recipients need to be vaccinated for several years after a successful transplant.

Measles are a rare complication in stem cell recipients. However, due to a (most likely unwarranted) fear of the vaccine’s side effects, an increasing proportion of parents avoid vaccinating their children. This will increase the risk of measles outbreaks, and smaller or larger outbreaks have been reported in several countries including Italy and the United Kingdom. Therefore, ensuring protection against measles might become increasingly important in the years ahead.

**Travel Recommendations**

The epidemiology of many of the diseases and vaccines discussed in the review differs around the world. Therefore, physicians counseling patients before international travel must be aware of the potential increased risk for both infection and severe disease among those who have undergone a stem cell transplant. Such counseling might include a recommendation to delay or avoid travel to certain destinations or to change the vaccination schedule (eg, starting a diphtheria, tetanus, and polio schedule before the recommended time of 12 months posttransplant). Indeed, the EBMT recommends starting these vaccinations between 6 and 12 months posttransplant in light of similar responses that have been demonstrated.[3]

**Disclosures:** The author(s) have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

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[1] http://www.diagnosticimaging.com/review-article