Varicella zoster virus vaccine in patients with haematological malignancies

Published Online
August 6, 2019
http://dx.doi.org/10.1016/S1473-3099(19)30400-1

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Reactivated varicella zoster virus disease is a painful and potentially severe infectious complication of immunosuppression that, for example, can affect patients with cancer.[1–3] An effective zoster vaccine has been used in elderly people for several years, but there is a risk for severe side effects in immunocompromised people, and deaths have been reported.[4,5] More recently, a subunit vaccine was introduced and has been shown to be effective in the elderly population.[6] A randomised trial also showed effectiveness and safety of this vaccine in patients who had undergone autologous stem cell transplantation.[7] In *The Lancet Infectious Diseases,* Alemnew Dagnew and colleagues[8] present the results of a large, randomised, placebo-controlled study that included participants with haematological malignancies who were vaccinated with two doses of the adjuvanted recombinant subunit vaccine or placebo either during or after cancer therapy. Adverse events were more common in subunit vaccine recipients although most adverse effects were of mild-to-moderate intensity There were fewer herpes zoster cases among patients who had received two doses of the subunit vaccine compared with those who received placebo (two cases *vs* 14 cases), and a post-hoc analysis showed a protective efficacy of 87·2% (95% CI 44·3–98·6; p=0·0021) against herpes zoster. Thus, the vaccine was considered generally safe and efficacious in eliciting a potentially protective immune response in people with haematological malignancies.

What are the potential implications of this study? It is important to understand that many patients with hematological malignancies are in an age group with an increased risk for herpes zoster, and this risk is further increased by the presence of malignancy. Therefore, a safe and effective zoster vaccine would be a valuable addition to the supportive care of these patients. Thus, the results of this study,[8] although not designed to primarily detect a decrease in the risk for herpes zoster, seem to support a protective effect and the authors conclude that the adjuvanted recombinant zoster vaccine is likely to benefit immunocompromised patients with haematological malignancies. However, there are caveats. First, this study had a short follow-up of only around a year after the second dose of the vaccine. This limitation is noted by the authors.[8] Another limitation is that the groups of participants with haematological malignancies included in the study were diverse, with some patients receiving short courses of intensive therapy, such as those with acute myelogenous leukaemia, and others having chronic malignancies, which are likely to require therapy for a long time. This variation is illustrated by the fact that a third of participants were vaccinated during immunosuppressive therapy and two-thirds were vaccinated after finishing immunosuppressive therapy.[8] Furthermore, patients who had undergone either autologous or allogeneic stem cell transplantation were also included. These different patient groups are likely to require different vaccine strategies, and this was not evaluated by the study.

Another caveat is that there was no standardised antiviral prophylactic regimen in the study.[8] There was no difference in the proportion of patients receiving prophylaxis, at around 30% of participants in each group. However, the authors do not report whether there were any differences in the durations of antiviral prophylaxis between the vaccine and placebo group and whether this affected the risk of herpes zoster. Aciclovir or valaciclovir prophylaxis is safe and usually effective against varicella zoster reactivation but an important question for clinicians managing immunocompromised patients is how long it should be given for.[9–11] A possible patient management strategy would be to give antiviral prophylaxis during the most intensive immunosuppressive treatment periods and then use an effective and safe vaccine to prevent later varicella zoster virus reactivations.

Where do we go from here? Should the vaccine be routinely administered in patients with hematological malignancies? The body of evidence on vaccine efficacy and safety in immunocompromised patients has increased with this study by Dagnew and colleagues.[8] Thus, it seems logical that elderly patients with hematological malignancies, who have an indication for herpes zoster vaccination on the basis of age, could safely receive the adjuvanted recombinant vaccine. However, it is unclear if additional doses will be needed

to maintain an immune response. Additional studies are needed to address the relative roles of this vaccine and antiviral prophylaxis and when best to apply different preventive strategies against varicella zoster reactivation in immunocompromised patients with haematological malignancies.

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PL reports grants from Merck Sharp & Dohme, personal fees from AiCuris, and grants from Shire, outside the submitted work.

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Herpes zoster in people who are immunocompromised: what are the options for prevention?

Published **Online** August 6, 2019 http://dx.doi.org/10.1016/S1473-3099(19)30399-8

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"Of all the classical precipitants of zoster, two—leukaemia and x-rays—are at present the most important", said R Edgar Hope-Simpson in 1965.[1] The link between compromised immunity and herpes zoster has been recognised for more than half a century. Individuals who are severely immunocompromised due to immunosuppressive conditions or therapies have herpes zoster more frequently and severely than the general immunocompetent population. Herpes zoster incidence per 1000 person-years at risk is reported to be 43·03 in adults with bone-marrow or stem-cell transplants, 17·04 in adults with solid organ transplants, and 17·43 in adults with HIV, compared with 4·82 in the general population.[2] Complications of herpes zoster are also roughly three times higher in people with HIV than in an age-matched general population.[3] Furthermore, severe immunocompromise is a contraindication to receiving live attenuated varicella zoster virus vaccine because of the potential risk of the vaccine virus replicating to cause disease.Preventing herpes zoster and its complications in individuals who are severely immunocompromised, therefore, remains an important public health goal.

In *The Lancet Infectious Diseases*, Kathleen Mullane and colleagues[4] report promising efficacy and safety of a γ irradiation-inactivated varicella zoster virus vaccine (v0ka strain) in patients with solid tumour malignancies receiving chemotherapy. In the randomised, double-blind, placebo-controlled, phase 3 trial done across 40 countries, the primary endpoint—herpes zoster incidence—was markedly reduced in patients with solid tumour malignancies receiving vaccine compared with those receiving placebo (22 *vs* 61 cases; vaccine efficacy 63·6%, 97·5% CI 36·4 to 79·1). These results came from 2678 patients with solid tumour malignancies on chemotherapy followed up for a mean of 2·45 years (SD 1·52) who each received at least one dose of the vaccine (the modified intention-to-treat population). The vaccine did not, however, reduce herpes zoster incidence in 2552 patients with haematological malignancies who received at least one vaccine dose (vaccine efficacy 16·8%, 97·5% CI –17·8 to 41·3).

The vaccine was well tolerated in patients with solid tumour malignancies receiving chemotherapy, with no differences between groups in frequencies of serious