Response to: 'Bivalent HPV vaccine safety depending on subtypes of juvenile idiopathic arthritis' by Dr Akioka

We thank Dr Akioka for the comments[1] on our recent study on the bivalent human papillomavirus (HPV) vaccine in patients with juvenile idiopathic arthritis (JIA).[2] Akioka and coworkers describe a patient with enthesitis-related JIA after receiving the bivalent HPV vaccine. It was unclear whether this patient newly developed JIA or experienced a flare of pre-existing JIA.

With regard to the former, vaccinations are indeed often described as potential environmental triggers inducing autoimmune diseases in genetically susceptible individuals.[3 4] For example, cases of systemic lupus erythematosus have been described after the quadrivalent HPV vaccine.[5] However, in a large register-based cohort study, including 997 585 girls among whom 296 826 received a total of 696 420 quadrivalent HPV vaccine doses, no association between exposure to the quadrivalent HPV vaccine and autoimmune adverse events was found.[6] Thus, large controlled studies often do not support a relation between vaccinations and the induction of autoimmune diseases except for the Guillain–Barré syndrome after the swine-flu vaccine and the oral polio vaccine, and idiopathic thrombocytopenia after the measles, mumps, rubella (MMR) vaccine.[7] Nevertheless, the involvement of vaccinations in the pathogenesis of autoimmune diseases deserves further study, as it can improve our understanding of immunopathogenesis and thereby contribute to the prevention of disease. By no means the (alleged) association between vaccinations and autoimmune diseases should result in refraining from current immunisation practice, because the actual prevalence of autoimmune reactions to vaccinations is remarkably low, their course is often milder than those associated with natural infections and we cannot identify the individuals who are at risk of developing an autoimmune reaction after vaccination. Therefore, the benefits of infection prevention outweigh the small risk of developing an autoimmune disease in genetically susceptible individuals.

With regard to the induction of JIA disease flares after vaccination, case reports exist of JIA flares after rubella or influenza vaccination.[7] Drawing conclusions from these case reports is impossible, because JIA has a relapsing and remitting disease course. To distinguish between a causal or temporal relation between vaccination and JIA disease flares, a (randomised) controlled study design is needed to correct for this relapsing disease course. We recently showed in a randomised controlled study that the MMR vaccination did not aggravate JIA.[8] In the current study involving the HPV vaccine, patients served as their own controls in order to detect potential aggravation of JIA disease after vaccination. No detrimental effect of HPV vaccination on JIA disease activity was detected, not even in patients with high baseline disease activity, or patients using methotrexate or anti-tumour necrosis factor-α.

Aikoka points out that patients with JIA reported longer durations of arthralgia, fatigue and headache after vaccination compared with healthy controls and fear that JIA patients are more at risk for (severe) adverse events after HPV vaccination. However, we also show that the frequency of these complaints was similar in patients and healthy controls and was transient within 2 weeks in all cases. We therefore conclude that patients with JIA and healthy controls tolerated the HPV vaccine equally well.

Aikoka suggests that polyenthesitis is an important factor in developing pain and adverse events caused by HPV vaccination, based on the fact that three patients developed inflammatory bowel disease (IBD), one uveitis and one lower back pain (of a non-inflammatory cause). We included only one patient with enthesitis-related JIA in this study. This patient did not develop severe adverse events. The four HLA-B27-positive patients also did not develop severe adverse events. We cannot draw conclusions on the risk of adverse events in enthesitis-related JIA because of these small patient numbers. Most importantly, we do not believe that these serious adverse events were related to the HPV vaccine, because the patients diagnosed with IBD already had abdominal pain, diarrhoea and intermittent rectal bleeding prior to the first HPV vaccine dose. Similarly, the treatment for uveitis in one oligoarticular JIA patient had been planned prior to HPV vaccination.

Although the serious adverse events in our study were in our opinion unrelated to HPV vaccination, we agree with Aikoka that it is important to remain vigilant for (severe) adverse events and to detect patients who are prone to develop (severe) adverse events after (HPV) vaccination. More studies are needed to discover means to identify patients who are individually predisposed to disease flares after vaccination. This might enable more personalised vaccination strategies in future.

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