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# RECOMBINANT ZOSTER VACCINE (SHINGRIX): A NEX GUN FOR RHEUMATOLOGIST

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Herpes Zoster, or as commonly known shingles, is a debilitating painful rash occurring at any age in anyone caused by reactivation of the varicella zoster virus (VZV).

After VZV infection, the virus establishes lifelong latency in the dorsal root neural ganglia and its reactivation can occur when the immune system is suppressed. The lifetime risk of HZ in the general population is around 30%,

In Italy, overall annual HZ incidence is 6.46 cases per 1,000 person–years (PY) in individuals ≥ 50 years of age[1]. HZ incidence increases with age and is estimated that 90% of adults have contracted VZV and is, therefore, at risk of developing HZ; further, at least 1 in 3 individuals will develop the disease in their lifetime[2-4]. Increased HZ incidence, attributed to a decline in immunity, is observed in elderly people and in patients using immunosuppressive medications.

In frail people, HZ and its complications can lead to an inability to regain the lifestyle, interests, and activity level that existed before its development leading to considerable morbidity and lower quality of life. Postherpetic neuralgia (PHN), the most feared complication of HZ, defined as chronic and debilitating pain that persists for at least 3 months (>90 days), can affect up to 30% of subjects[2]. Individuals with HZ or HZO (Herpes Zoster Ophthalmica) have a 1- to 4-fold increased risk of cardiovascular and cerebrovascular events (myocardial infarction/cerebral stroke)[5].

Both HZ incidence and HZ related complications occur more frequently and with higher severity in immunocompromised patients[6], in whom visceral involvement (meninges/brain, lungs, liver) may also be observed[2].

Patients with rheumatoid arthritis (RA) have a cumulative relative risk of contracting HZ of 51%[6].

Patients receiving biologic drug therapy (bDMARD), compared with the control population or without therapy, have a 71% increased risk of HZ[7,8].

JAK inhibitors have been linked with an increased risk of herpes zoster (HZ). So, in patients using JAK inhibitor drugs, the development of HZ is an emerging complication.

In patients treated with tofacitinib, the risk of developing HZ was twice as high as in patients with RA undergoing biologics. Tofacitinib is also associated with a 3-fold increased risk of HZ compared with TNF-α inhibitors[9]. In the UPA phase III RA clinical programme, which included 5306 patients with RA, the rate of HZ was higher in patients with UPA (Upadacitinib) compared with MTX monotherapy or adalimumab + MTX, and higher with the 30 mg *vs.* 15 mg dose[10].

SLE patients have 150% increased risk of HZ (RR=2.50; 95% CI 2.36, 2.65). A systematic review with meta-analysis by Reigosa et al[11] showed that a combined use of immunosuppressants in patients with SLE increases the risk of HZ 5- to 17-fold for 1 or ≥ 4 drugs taken in combination therapy, respectively.

Patients with SLE have a 127% additional risk (RR=2.27; 95% CI 1.75-2.94) of developing postherpetic neuralgia at 3 months after the onset of HZ [12]. In patients with chronic renal failure and SLE comorbidities, a flare-up from HZ may lead to an additional risk of ERSD of 51% (aHR=1.51; 95% CI 0.34, 6.72)[13].

In light of the significant burden caused by HZ and its complications in frail patients, adopting a preventive strategy seems promising, particularly using vaccination in appropriate age and risk groups. Until now, a live attenuated vaccine (ZVL) indicated for immunization of individuals 50 years of age and older and contraindicated in immunocompromised individuals was available in Italy, which was able to reduce cases of PNH by around 65%, and about 50% of all clinical cases of HZ. The demonstrated efficacy in preventing cases of HZ decreases with age, from 70% in 50-year-olds to 41% in 70-year-olds[14].

As reported in the Ministerial Circular dated March 8, 2021 (0008770-08/03/2021-DGPRE-MDS-P), a new recombinant adjuvanted -RZV vaccine against HZ is now available in Italy through the public channel, indicated in people 65 years of age and older and in individuals at increased risk of HZ from 18 years of age[14].

ZOE-50 and ZOE-70 were two phase 3 trials that demonstrated a clinical efficacy of RZV in preventing HZ cases >90% in all age groups above 50 and 70 years, respectively[15,16]. Efficacy higher than 90% was shown to persist at least over the 7 years of follow-up; furthermore, efficacy in preventing post-herpetic neuralgia and other complications > 90% was also demonstrated[17].

Moreover, RZV has a high safety profile, most post-vaccination reactions were mild to moderate and of short duration. The most frequently reported side effects were injection site pain, myalgia, fatigue, and headache, and no increase in serious adverse events or immune-mediated conditions was reported compared with placebo[18].

A pooled post hoc analysis of the ZOE-50 and ZOE-70 clinical trials, in adults with pre-existing potential immune-mediated diseases showed a clinical efficacy >90% and a good safety profile in this group of patients with a rate of serious adverse events similar to the placebo group[19].

A further study in 403 patients with rheumatoid arthritis and other systemic rheumatic diseases who received the RZV vaccine demonstrated the safety of RZV vaccine in such patients, in fact the incidence of disease flares was 7% or less and that of side effects was 13%, both less than the clinical trials data [20].

The RZV vaccine cycle involves the administration of two doses; the second dose can be administered within a time frame of 2 to 6 months after the first dose. In subjects for whom a condition of immunodepression due to therapy or disease is expected, the second dose of Shingrix can be administered 1 to 2 months after the initial dose [18].

The EULAR Guidelines, in view of the fact that AIIRD patients are at higher risk of HZ than the general population, with the highest risk of infection in patients with inflammatory myositis and SLE of all ages, recommend anti-zoster vaccination by emphasizing that the new non-live recombinant subunit vaccine proved to be safe and more effective than the live-attenuated vaccine in older adults. Further, it can be used in immunocompromised patients as opposed to the live vaccine[21].

Given the availability in Italy of the new recombinant adjuvanted anti-Herpes Zoster (RZV) vaccine, we believe it is useful to vaccinate patients with autoimmune diseases with this vaccine in line with principle guidelines. So far data demonstrate the efficacy and safety of RZV vaccine in rheumatologic patients with low incidence of flares of disease and side effects; however, more specific immunogenicity, efficacy and safety studies are urgently needed evaluating these parameters in different groups of medications and different drugs and also analysing long term protection. As for COVID-19 vaccination, the temporary interruption of some rheumatologic medication may be explored to increase efficacy and length of protection of RZV, nevertheless taking into account the possibility of a flare of disease.

**Conflict of interest:**

The authors declare no conflict of interest.

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