INTRODUCTION

Herpes Zoster (HZ) is a blistering, painful and disabling cutaneous rash that can occur in any type of patient at any age. It is caused by reactivation of the Varicella Zoster Virus (VZV). Autoimmune inflammatory rheumatic diseases (AIIRDs) are associated with an increased risk of infections due to use of corticosteroids, comorbidities, the immunosuppressive effect of AIIRDs themselves and of the drugs used to treat them. In light of the clinical and psychological effects of HZ and its complications in affected patients, it is essential to carry out a prevention strategy by implementing vaccination programs in appropriate age and high-risk groups, given also the availability of the new recombinant adjuvanted anti-Herpes Zoster (RZV) vaccine in Italy. The College of Italian Rheumatology think it is useful to share some scientific data on the epidemiological and clinical impact of HZ in patients with AIIRDs and on the current national vaccine availability.

KEYWORDS: Infection, Autoimmune rheumatic diseases, Vaccine, Herpes zoster.
Autoimmune inflammatory rheumatic diseases (AIIRDs) are associated with an increased risk of infections due to use of corticosteroids, comorbidities, the immunosuppressive effect of AIIRDs themselves and of the drugs used to treat them, namely conventional synthetic disease-modifying antirheumatic drugs (DMARDs), biotechnological (b-) and small molecule DMARDs.

In light of the clinical and psychological effects of HZ and its complications in affected patients, it is essential to carry out a prevention strategy by implementing vaccination programs in appropriate age and high-risk groups. Given the availability of the new recombinant adjuvanted anti-Herpes Zoster (RZV) vaccine in Italy, we believe it is useful to share some scientific data on the epidemiological and clinical impact of HZ in patients with AIIRDs and on the current national vaccine availability.

EPIDEMIOLOGY

• It is estimated that given that 90% of adults contracted VZV, they are at risk of developing HZ and that at least 1 in 3 individuals will develop the disease in their lifetime\(^1\,^2\);
• In Italy, the incidence of HZ is 6.46/1000 person-years in subjects ≥ 50 years of age\(^3\).

COMPLICATIONS

• Postherpetic neuralgia (PHN) is the most feared complication of HZ. Defined as chronic and debilitating pain that persists for at least 3 months (> 90 days) after HZ, it can persist for months or even years and can affect up to 30% of patients\(^2\);
• In the case of ophthalmic herpes zoster (OHZ), acute and chronic local ocular complications may occur up to and including blindness;
• Individuals affected by HZ and in particular OHZ have a 1 to 4 times increased risk of cardiovascular and cerebrovascular events (myocardial infarction/stroke)\(^4\);
• Symptoms and complications may be more severe and long-lasting in immunocompromised patients\(^5\,^6\), in whom visceral involvement (meninges/brain, lungs, liver) may also occur\(^1\).

CLINICAL IMPACT IN RHEUMATOLOGIC PATIENTS

• Patients with rheumatoid arthritis (RA) have a cumulative relative risk of contracting HZ of 51%\(^9\);
• Patients receiving biological therapy (bDMARD) compared to the rheumatological population without therapy or controls have a 71% increased risk of contracting HZ\(^10\);
• In patients taking JAK inhibitors, the development of HZ is an emerging and relevant complication. In patients treated with tofacitinib, the risk of developing HZ was double that of RA patients taking bDMARDs. Tofacitinib is also associated with a 3-fold higher risk of HZ than TNF-α inhibitors\(^11\). In the UPA phase III RA clinical trial, which included 5306 patients with RA, the rate of HZ was higher in patients taking UPA (Upadacitinib) than in those taking methotrexate (MTX) in monotherapy or adalimumab + MTX in combination, and higher with 30 mg dose vs. 15 mg dose of UPA\(^10\);
• Patients with systemic lupus erythematosus (SLE) have a 150% increased risk of HZ (RR = 2.50; 95% CI 2.36-2.65 in a systematic review with meta-analysis by Pego-Reigosa et al\(^12\)). The combined use of immunosuppressants in patients with SLE increases the risk of HZ by 5 to 17 times, respectively for 1 or ≥ 4 drugs taken in combination therapy\(^13\). Patients with SLE have an additional risk of 127% (RR = 2.27; 95% CI 1.75-2.94) of developing PHN after HZ onset\(^14\). In patients with chronic renal failure and SLE, the development of HZ may lead to an additional risk of end-stage renal disease (ESRD) of 51% (aHR = 1.51; 95% CI 0.34, 6.72)\(^15\).

VACCINATION SCHEDULE

The 2017-2019 National Vaccine Prevention Plan (PNPV, in Italian), for which an extension was requested until the approval of the new PNPV, introduced the free offer of anti-HZ vaccination for subjects\(^16\):
• > 65 years of age;
• >50 in the presence of diabetes mellitus, cardiovascular disease, COPD;
• Prescribed with immunosuppressive therapy.
Only a live attenuated vaccine (ZVL) was available in Italy up until recently. It was indicated for subjects from 50 years of age and contraindicated for immunocompromised patients. Data showed that it was capable of reducing PNH cases by about 65% and HZ cases by about 50%. The effectiveness demonstrated in the prevention of HZ cases decreased with age, going from 70% in subjects in their fifties to 41% in subjects in their seventies. The Ministry of Health Report of 8th March 2021 announced that a new recombinant adjuvanted vaccine (RZV) against HZ is now available in Italy. It is indicated for people aged >50 and in individuals at increased risk of HZ aged >18.

The most important scientific data about RZV are the following:

a. Clinical efficacy in the prevention of cases of HZ greater than 90% in all age groups >50 years;

b. Persistence of effectiveness of >90% for at least 7 years;

c. Effectiveness in the prevention of PHN and other complications of >90%;

d. Clinical Development Plan in immunocompromised subjects with: HIV, autologous hematopoietic stem cell transplantation (aHSCT), kidney transplantation, subjects with onco-hematological diseases and solid tumors. Immunogenicity data show that the adjuvanted recombinant vaccine stimulates a strong cellular and humoral immune response, and that clinical efficacy in aHSCT patients vaccinated at day 60 post-transplant was 68.2%17;

e. The safety profile is high, since 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 diseases was reported compared to placebo17;

f. RZV vaccination cycle involves the administration of two doses: the second dose can be administered from 2 to 6 weeks after the first dose. In individuals who are immunosuppressed due to therapy or disease, the second dose of RZV can be administered 1 to 2 months after the first one17.

The European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) Guidelines recommend the anti-zoster vaccination to their patients because patients with AllIRDs are at greater risk of HZ than the general population, with the highest risk of infection in patients of all ages with inflammatory myositis and SLE. The Guidelines underlined that the new recombinant protein-subunit adjuvanted vaccine, being safe and more effective than the live-attenuated vaccine in elderly adults, can be used in immunocompromised patients. Indeed, data so far demonstrate the efficacy and safety of RZV in rheumatological patients, with a low incidence of disease flare-ups and side effects.

Based on the aforementioned considerations, the CREI recommends vaccination with the new recombinant adjuvanted anti-Herpes Zoster vaccine (RZV) for patients with autoimmune diseases at high risk of developing HZ-related infection.

However, it is fundamental and compelling to carry out more specific studies evaluating immunogenicity, efficacy, and safety in patients with AllIRDs, evaluating patients taking different drugs (of different or same class) and analyzing long-term protection. As with COVID-19 vaccination, temporary discontinuation of some rheumatological drug could be explored to increase the efficacy and duration of RZV protection, always taking into account the possibility of disease relapse.

In consideration of the efficacy and safety profile of the new adjuvant recombinant vaccine, all Italian Regions have ensured a vaccination plan with specific methods and routes (Local healthcare service/Hospitals/General Practitioners). We, therefore, advice getting in contact with the Hygiene Office of the Local healthcare service (ASL). Physicians can recommend getting the RZV through a simple white prescription.

**KEY POINTS**

- Vaccination should be a personal, individualized decision: vaccination must be correctly explained to patients, illustrating risks and benefits, in order to provide a basis for a shared decision-making process between rheumatologist and patient;
- Taking into account what is done for all other vaccinations, we conditionally recommend RZV to be administered during disease quiescence (when possible);
- In all rheumatological patients, vaccination against HZ should preferably be considered before starting tsDMARDs or bDMARDs, in particular Rituximab;
- It does not seem necessary to withhold the dose of bDMARD or tsDMARD before vaccination with RZV, but further data is needed;
• In view of the depleting effect on B lymphocytes, it is conditionally recommended to administer the RZV one month before the start of Rituximab. For patients being treated with Rituximab, the vaccine should be given at least 6 months after the last dose and/or 4 weeks before the next dose of Rituximab;
• In patients taking a daily dose of prednisone or equivalent of ≤10 mg or >10 mg but <20 mg, no dose interruption or reduction is necessary;
• If the daily dose of prednisone is ≥20 mg it would be preferable to carry out vaccination after the dose has been reduced to <20 mg daily;
• Regardless of any previous episode of HZ, it would be useful to administer the two doses of RZV 2-6 months apart to all AIIRD patients about to start immunosuppressive therapy or already on therapy aged >18 years.

CONFICT OF INTERESTS:
The authors declare no conflict of interest.

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ETHICS COMMITTEE APPROVAL:
Not required

INFORMED CONSENT:
Not required

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