

# Herpes zoster in psoriasis patients undergoing treatment with biological agents: prevalence, impact, and management challenges

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**Abstract:** As TNF- $\alpha$  is a major factor in the immune defense against herpes zoster (HZ); an increased incidence and severity of HZ cases were suspected in patients undergoing treatment with TNF antagonists. Several studies and clinical experience provided evidence that the incidence of HZ increases by twofold to threefold in this patient category. The number of severe cases of HZ, with multisegmental, disseminated cutaneous, and/or systemic involvement, is also increased. Concerning psoriasis patients under biologicals, the clinician should be more alert for an eventual HZ event, in particular during the first year of biological treatment, and be aware of the possibility of more severe HZ cases. HZ may also undergo an age-shift toward younger patients. Rapid identification of risk factors for severe HZ, such as severe prodromal pains and/or the presence of satellite lesions, is recommended. The treatment recommendations of HZ in this patient group are identical to the recently published guidelines for the management of HZ. The live attenuated viral vaccine OKA/Merck strain anti-HZ vaccination is recommended before initiating biological treatment in psoriasis patients. The new adjuvanted anti-HZ vaccine will probably also benefit patients while on biological treatment.

**Keywords:** herpes zoster, TNF antagonists, anti-IL17, anti-IL12/23, psoriasis, aciclovir

## Introduction

Psoriasis is an inflammatory, predominantly skin disease, affecting ~1%–5% of the population and has a high impact on the patient's quality of life.<sup>1</sup> Moreover, severe and longstanding cases of psoriasis are often associated with a moderate-to-severe metabolic syndrome, potentially reducing the life expectancy by some years.<sup>1</sup>

Nowadays, moderate-to-severe plaque and patch-type psoriasis vulgaris can very effectively be treated with first-generation biologicals. They are represented by the TNF- $\alpha$ -antagonists,<sup>2</sup> including the receptor antagonist etanercept, a recombinant fusion protein that inhibits soluble and membrane-bound TNF- $\alpha$ <sup>3</sup>; the monoclonal chimeric antibody infliximab<sup>4</sup> that binds membrane-bound and soluble TNF- $\alpha$ ; and the human monoclonal antibody adalimumab that blocks TNF- $\alpha$  interactions with the p55 and p75 cell surface TNF receptors. The TNF- $\alpha$ -antagonists achieve PASI75 improvements in a high proportion of patients,<sup>5,6</sup> a significant improvement compared to the older psoriasis treatments such as methotrexate, acitretin, and ciclosporin.<sup>2</sup>

Although the overall safety records of TNF- $\alpha$ -antagonists are outstanding, there is evidence of an increased propensity to infections,<sup>7–10</sup> in particular viral infections. Among these, varicella zoster virus (VZV), herpes simplex virus, hepatitis virus infections, and viral infections affecting the ear–nose–throat region are the most common.<sup>11–13</sup>

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The second-generation biological agents for patch and plaque-type psoriasis include ustekinumab, which prevents the actions of IL-12 and IL-23 by binding to their mutual subunit p40<sup>14</sup>; secukinumab, a human IgG1 $\kappa$  monoclonal antibody that selectively binds and neutralizes IL-17A<sup>15,16</sup>; ixekizumab, a humanized IgG4 monoclonal antibody that neutralizes IL-17A<sup>17</sup>; and apremilast, a PDE4 inhibitor.<sup>18</sup> The safety assessments of the initial trials demonstrated a similar rate of viral infections compared to the placebo groups. This fact may be due to the relative recent introduction of these agents in clinical practice. Another hypothesis is that the targeted cytokine pathways are less important for antiviral host defense mechanisms.

The cutaneous eruption-termed herpes zoster (HZ) is a self-limiting, dermatomally localized, papulo-vesicular-pustular, and crusted eruption caused due to the reactivation of the VZV that remained dormant in the dorsal root ganglia after the primary contact with VZV in the form of chickenpox during childhood.<sup>19–21</sup> Approximately 1 million new cases of HZ are diagnosed each year in the USA.<sup>22</sup> Every year, 96 HZ-related deaths are reported, all diagnosed in elderly and/or immunocompromised patients.<sup>22</sup> The incidence of HZ is rising with increasing age, and in patients older than 60 years, there are approximately ten cases of HZ per 1,000 US population per year.<sup>22</sup> In patients aged between 35 years and 44 years, ~194 women and 261 men experience HZ per 100,000 population, with these values increasing to 1,624 women and 1,112 men in patients older than 75 years.

Severe and extensive cutaneous HZ, multidermatomal HZ, and even systemic dissemination of VZV are the major complications of HZ. Especially, the immunocompromised population, including HIV patients, organ and bone marrow transplant recipients, and patients under immunosuppressive medication, is at risk for these complications.<sup>19–21</sup>

Postherpetic neuralgia (PHN) is the most feared complication following the resolution of the cutaneous lesions of HZ. The precise pathomechanisms are still not totally elucidated. The incidence of PHN also rises with increasing age. The risk of PHN is increased with, among the most important factors, age, severe cutaneous HZ, female sex, and/or severe prodromal pains.<sup>19–21</sup> The term zoster-associated pain is used to describe the entire pain spectrum of HZ, including the prodromal and concomitant pains as well as the PHN.

TNF- $\alpha$  is a major factor in the host immune response against HZ.<sup>23,24</sup> Consequently, TNF- $\alpha$  antagonists could increase the risk and the severity of HZ. Indeed, since the earliest use of TNF- $\alpha$  antagonists, severe cases of HZ have continuously been reported.<sup>25</sup> In contrast, for secukinumab,

ixekizumab, and apremilast, not directly interfering with the TNF- $\alpha$  pathway, no reports have been published, until today, concerning severe HZ eruptions during treatment.

From the clinician's point of view, five major questions arise in relationship to the management of HZ in psoriasis patients under biological agents:

1. Is the incidence of HZ increased in psoriasis patients receiving biological agents?
2. Is the severity of HZ increased in psoriasis patients under biological agents?
3. Are the incidence and severity of PHN increased in psoriasis patients under biological agents?
4. Is anti-HZ vaccination indicated in patients before or while on biological treatment?
5. What are the recommendations in terms of management of HZ in patients with psoriasis receiving biologicals?

## Is the incidence of HZ increased in psoriasis patients receiving biological agents?

This question is most frequently addressed by studying the crude incidence rates (CIRs) calculated by drug exposure and Cox proportional hazard models evaluating the adjusted association between a biological agent and the HZ event.

In general, these studies demonstrated that the exposition to biologicals increases the risk of HZ twofold to threefold, independent of whether these studies were dealing with inflammatory joint diseases,<sup>11,26–35</sup> inflammatory intestinal bowel diseases,<sup>36,37</sup> or inflammatory skin diseases.<sup>12,30,38–40</sup> Whether there is a specific drug-associated risk remains still debated. An overview, including several cohort studies, randomized controlled trials, and case reports, suggested that infliximab conferred an increased risk of HZ, whereas adalimumab, etanercept, and ustekinumab did not. However, data still remain controversial. In sum, no specific biological agent seems to exhibit a particular HZ risk compared to another.<sup>12</sup> Interestingly, the patients seem to be more at risk of developing HZ during the first months of treatment<sup>41</sup> and the time to HZ seems to be shortened in patients treated with TNF- $\alpha$  antagonists.<sup>34</sup>

However, incidence data should be interpreted with caution for various reasons: the incidence of HZ increases progressively with age, a parameter often neglected in studies, and the study populations are extremely heterogeneous in many respects (previous exposure to one or more disease-modifying antirheumatic drugs and duration of exposure, previous exposure to other biological agents and duration

of exposure, other concomitant immunosuppression, other concomitant medication, combination therapies, etc).

Psoriasis is probably not different in terms of risk for HZ during biological treatment compared to the other inflammatory rheumatologic or gastrointestinal diseases. However, only a small number of studies specifically addressed this issue of psoriasis patients.<sup>12,38,39</sup>

An Israeli study evaluated the incidence of HZ among psoriasis patients treated with phototherapy, traditional systemic medications, and biological drugs. The incidence rates of HZ were calculated for each medication, and hazard ratios were adjusted for age, sex, and health care utilization burden. This study, which included a total of 22,330 psoriasis patients accounting for 215,656 patient years (py), revealed 1,321 cases of HZ. The CIRs were the following: 6.0 for ultraviolet B phototherapy (95% confidence interval [CI]: 0–12.8), 10.1 for psoralen and ultraviolet A (95% CI: 1.3–19), 5.4 for acitretin (95% CI: 2.2–8.7), 17 for methotrexate (95% CI: 10.6–23.4), 13.9 for etanercept (95% CI: 0.3–27.4), 19.3 for infliximab (95% CI: 0–45.8), and 4.6 for controls (95% CI: 4.3–5) per 1,000 py. No case of HZ was observed among patients treated with alefacept, efalizumab, or adalimumab. A multivariate analysis demonstrated that age, female sex, health care utilization pattern, and corticosteroid treatment were all associated with the time to HZ. Only the association of HZ with infliximab treatment approached statistical significance (hazard ratio: 1.77, 95% CI: 0.92–3.43).<sup>38</sup> The authors concluded that some biological drugs were associated with a higher incidence of HZ compared with controls, although not statistically significant.<sup>38</sup> Another study included a total of 1,220 eligible patients on biologicals, representing 4,206 py. The CIR per 1,000 py was 5.2 (95% CI: 3–7.4). Eleven HZ cases occurred during adalimumab treatment (CIR 7.1 per 1,000 py, 95% CI: 2.9–11.3), four during etanercept treatment (CIR: 5.1 per 1,000 py, 95% CI: 0.1–10), four during infliximab treatment (CIR: 2.4 per 1,000 py, 95% CI: 0–4.7), two during ustekinumab treatment (CIR: 53.5 per 1,000 py, 95% CI: 0–125.6), and one during rituximab treatment (CIR: 5.2 per 1,000 py, 95% CI: 0–17.6). The incidence was higher for patients older than 60 years in this study, compared to that of the general population, although not statistically significant. Fourteen cases of HZ were observed in patients suffering from chronic inflammatory joint disease (14/737=1.89%), five in those suffering from psoriasis (5/238=2.1%), and three in those suffering from chronic inflammatory intestinal disease (3/360=0.83%).<sup>39</sup> Specifically assessing psoriasis patients, three cases of HZ were observed during etanercept treatment in 200 py, three cases of HZ during infliximab treatment in 166 py, zero cases of HZ during adalimumab treatment in 325 py, and

two cases of HZ during ustekinumab treatment in 26 py.<sup>39</sup> In total, five cases of HZ were observed during a total of 717 py (0.7%) in psoriasis patients.

Consequently, considering that ~1 million patients will experience HZ each year in a total USA population of 320 million,<sup>22</sup> representing 0.3125% of the population, it seems that biological treatments for psoriasis increase the risk of HZ by approximately twofold.

## Is the severity of HZ increased in psoriasis patients under biological agents?

In the majority of psoriasis patients undergoing biological treatments, the course of HZ will not differ from HZ observed in a normal, nonimmunocompromised, age-matched population in terms of severity. However, the risk and incidence of severe HZ clearly increase in this population. Indeed, some of the patients may present very severe HZ in terms of cutaneous extension inside the involved dermatome(s), multidermatomal involvement in adjacent dermatomes and nonadjacent dermatomes, and increased duration of the HZ skin lesions (Figures 1 and 2).<sup>26–29,38,39,42,43</sup> In a study that identified 86 cases of HZ among 82 patients under biologicals, multidermatomal HZ was observed in 18.3% of patients,



**Figure 1** Severe and extensive multidermatomal unilateral HZ of the sacral dermatomes occurring during the use of TNF antagonists for psoriasis.

**Note:** Photo courtesy of Professor Nikkels.

**Abbreviation:** HZ, herpes zoster.



**Figure 2** Severe multisegmental HZ in an elderly woman using TNF antagonists for psoriasis.

**Note:** Photo courtesy of Professor Nikkels.

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HZ ophthalmicus in 4.9%, and hospitalization due to severe disease in 14.6%. Complications were reported in three patients.<sup>28</sup> In another study, bidermatomal and multidermatomal HZ were observed in 45% and 32% of the HZ patients, respectively. Furthermore, two patients presented with a protracted course (>4 weeks) of cutaneous VZV infection.<sup>39</sup>

It is not determined whether the cases of severe HZ were associated with a specific biologic agent. Currently, clinical experience cannot attribute a specific risk to any particular biological agent. Aside from potential severity, in this patient group, no distinctive clinical features of HZ were noted compared to common HZ.

### Are the incidence and severity of PHN increased in psoriasis patients under biological agents?

In the general population older than 50 years, the incidence of PHN is ~2%–9% at 3 months after the resolution of the HZ skin lesions.<sup>19–21</sup> Subsequently, the rate of PHN decreases progressively over months. TNF- $\alpha$  has been implicated in the pathogenesis of neuropathic pain. Higher circulating levels of 1 $\beta$ , IL-6, IL-8, IL-10, and TNF- $\alpha$  during HZ were measured compared to controls. Although IL-6 was significantly higher in HZ patients evolving to PHN, there was no clear link between elevated TNF- $\alpha$  levels and PHN.<sup>44</sup> The effect of biological treatments on the incidence and severity of PHN remains debated. One study that included 1,220 patients (4,206 py) receiving first-generation biologicals revealed that PHN, persisting for more than 6 months, in 20% of the HZ patients,<sup>39</sup> was significantly higher compared to the

general population. In contrast, in another patient group, only 2.4% of the patients under biologicals experienced PHN.<sup>28</sup> Another study that included 206 patients presenting HZ while on TNF- $\alpha$  inhibitors only diagnosed PHN in <1% of the patients.<sup>45</sup>

Hence, the precise impact of PHN on the first-generation biological treatments for psoriasis remains nonelucidated. No data are available for the second-generation biologicals.

### Is anti-HZ vaccination indicated in patients before or while on biological treatment?

Owing to the increased incidence and risk of severe HZ, vaccination against HZ seems a reasonable medical attitude. Vaccination against HZ aims to boost the VZV-specific cell-mediated immunity. VZV-specific cell-mediated immunity is acquired during varicella and subsequently progressively wanes over the years until a threshold value is reached that allows VZV reactivation in the dorsal root ganglia, finally leading to HZ.

The current HZ vaccine is a more concentrated (~14-fold) form of the varicella vaccination OKA/Merck strain (Zostavax). This vaccine is a live attenuated viral vaccine (LAVV). Although highly efficacious with a 66.5% reduction in PHN ( $P<0.001$ ) and a 51.3% ( $P<0.001$ ) reduction in the incidence of HZ,<sup>46</sup> it is theoretically contraindicated to administer this type of vaccine during the use of TNF antagonists and other biological agents. However, in a retrospective cohort including 463,541 Medicare beneficiaries older than 60 years with rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, or chronic inflammatory bowel diseases, the overall CIR of HZ was 7.8 cases per 1,000 py in the group having received the HZ vaccine and the rate among the unvaccinated was 11.6 cases per 1,000 py. Among the 633 patients exposed to biologicals at the time of vaccination, no single case of HZ occurred.<sup>47</sup> Despite these reassuring results, it remains cautious to refrain from vaccinating with an LAVV system while on biologicals.

Recently, the efficacy and safety of a new adjuvanted HZ subunit vaccine containing the VZV glycoprotein E and the AS01B adjuvant system have been evaluated in a randomized, placebo-controlled, multicenter, Phase III study that included 15,411 adults older than 50 years of age and stratified according to age groups (50–59 years, 60–69 years, and older than 70 years).<sup>48</sup> During a mean follow-up period of 3.2 years, HZ was confirmed in six participants among the 7,698 vaccinated volunteers (CI: 0.3 per 1,000 py) and in 210 participants

among the 7,713 volunteers comprising the placebo group (CI: 9.1 per 1,000 py). The overall vaccine efficacy against HZ was 97.2% (95% CI: 93.7–99;  $P < 0.001$ ). The efficacy of the vaccine in adults older than 70 years was similar to that observed in the younger age groups.<sup>48</sup> The major advantage of this type of vaccine is that patients receiving biologicals are allowed to be vaccinated.

In sum, it is advisable to administer the LAVV-type anti-HZ vaccine before initiating biologicals for psoriasis patients older than 50 years.<sup>49–52</sup> For patients already under biologicals, the adjuvanted vaccine type will probably be recommended when commercially available.<sup>49</sup>

## What are the recommendations in terms of management of HZ in patients with psoriasis receiving biologicals?

All the studies demonstrated that all the patients experiencing HZ responded positively to antiviral treatment, even the more severe cases. Resistant VZV strains were never encountered.

The treatment recommendations for HZ are not different from those for immunocompetent patients.<sup>49</sup> Oral antiviral medication (acyclovir [ACV] 800 mg, five times per day for 7 days; valaciclovir 2×500 mg, three times per day for 7 days; famciclovir 500 mg, three times per day for 7 days; or brivudin 125 mg/d for 7 days) is recommended for the subgroups of patients listed in Table 1. Intravenous administration of ACV (10 mg/kg/8 h for 7 days at least) is suggested for patients with complicated HZ or who are at a high risk of complicated HZ (Table 2).<sup>49</sup> Antiviral treatment should be initiated as soon as possible (<72 hours after the appearance of skin lesions). For ACV, famciclovir, and valaciclovir, the renal function should be tested before administration and dosages should be reduced in the case of renal insufficiency. The association of fluorouracil and brivudin should absolutely be avoided.

**Table 1** Indications of oral antiviral medication

HZ of any localization in patients older than 50 years
Facial and/or cervical HZ
HZ of any localization with
Moderate-to-severe ZAP
Hemorrhagic or necrotizing lesions
Multidermatomal involvement
Abnormal vesicles/presence of satellite lesions
Involvement of mucous membranes
HZ in immunocompromised patients
HZ in patients with predisposing skin diseases (such as atopic dermatitis)

**Abbreviations:** HZ, herpes zoster; ZAP, zoster-associated pain.

**Table 2** Indications of intravenous administration of ACV as suggested for patients with complicated HZ or who are at a high risk of complicated HZ

HZ of the head and/or neck area, particularly in elderly patients
HZ with hemorrhagic/necrotizing lesions, multisegmental involvement, abnormal vesicles/satellite lesions, or involvement of mucous membranes or generalized HZ
HZ in immunocompromised patients
HZ with signs of visceral or central nervous system involvement

**Abbreviations:** ACV, acyclovir; HZ, herpes zoster.

No specific diagnostic techniques to prove the diagnosis of HZ are indicated for common HZ of the trunk.<sup>53</sup> In contrast, HZ of the orofacial and anogenital area should be differentiated from zosteriform herpes simplex virus infections.<sup>53</sup>

Although it is not possible to predict the severity of HZ in a given patient, the presence of satellite lesions at the beginning of the HZ eruption and the presence of a very painful prodrome are helpful clinical indicators for an increased risk of severe HZ.<sup>54</sup>

## Conclusion and recommendations

Concerning HZ in psoriasis patients receiving biologicals, the following statements are proposed:

- Psoriasis does not confer a specific higher risk of HZ compared to the other inflammatory joint and intestinal diseases.
- The administration of biologicals in these patient groups increases the incidence of HZ by twofold to threefold.
- In patients treated with biologicals, one may expect HZ in younger age groups compared to common HZ.
- One should be more vigilant for a possible diagnosis of HZ in the first year after the instauration of a biological therapy.
- HZ is usually not different from common HZ in the immunocompetent population.
- Very severe and extensive cases of HZ are rare in these patient groups.
- In the case of HZ, look for risk factors for severe HZ, especially satellite lesions and severe prodromal pains.
- Antiviral treatment and management of HZ in psoriasis patients under biologicals are not different compared to their nonimmunocompromised counterparts.
- Intravenous ACV treatment is recommended for severe cases of HZ.
- If possible, the HZ LAVV vaccine should be administered before starting biologicals in patients never having experienced HZ previously.

- When commercially available, the new subunit HZ vaccine should be provided before or during biological treatments in patients never having experienced HZ previously.

## Disclosure

The authors report no conflicts of interest in this work.

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