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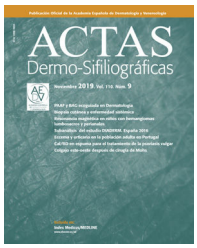

CASE AND RESEARCH LETTER

# JAK Inhibitors in Atopic Dermatitis Associated With Risk of Viral Infections: A Critical Appraisal

## Inhibidores de JAK en dermatitis atópica asociados al riesgo de infecciones virales: evaluación crítica

*To the Editor,*

Atopic dermatitis (AD) is one of the commonest inflammatory dermatoses. AD related cytokines such as IFN-γ, IL-4, IL-13, IL-31, IL-33, IL-23, IL-22, and IL-17 have downstream signalling through Janus kinase (JAK) signal transducer and activator of transcription (STAT) pathway. JAK inhibitors have shown to decrease the symptoms and severity of AD. Albeit, JAK inhibitors are not approved by the United States Food and Drug Administration (U.S. FDA) for the treatment of AD. JAK inhibitors such as abrocitinib, upadacitinib, baricitinib (oral) and ruxolitinib, delgocitinib (topical) are currently in clinical trials for the treatment of AD.[1] Headache, nausea, nasopharyngitis are the common systemic adverse events seen with these agents. Viral infections and reactivation of herpes simplex virus (HSV), eczema herpeticum (EH), herpes zoster (HZ) are the dermatological adverse effects reported with JAK inhibitors. Shah et al.[2] described the vulnerability of AD patients on JAK inhibitors treatment to HSV infection, reactivation, EH and HZ.

Most of the data for HSV infection has been derived from tofacitinib which is FDA approved in rheumatoid arthritis, psoriatic arthritis and inflammatory bowel disease (IBD). However, there has been much less incidence of HSV infection, HZ and EH from the clinical trials of specified JAK inhibitors in AD.[3] It may be due to exclusion of patients with history of EH, HSV infection in the studies. Moreover, baricitinib has been approved in the European Union for AD in November 2020, but history of EH is not included as a contraindication.

The host adaptive response to viruses is directed mainly by Th1 cells. The main cytokines responsible for Th1 polarisation are interferon (IFN)-γ and interleukin (IL)-12 and the intracellular pathways of these are mediated by JAK 1-2/STAT1 and JAK 2-TYK2/STAT4 respectively.[4] The inhibition of JAK-3 and JAK-1 significantly inhibit the effective production of antibodies.[5] Both innate and acquired immunity are essential to generate response against viral infections. Therefore, JAK inhibitors in AD have every possible theoretical chance of virus infection, reactivation and dissemination. There is further increased chances of EH, HSV infection, reactivation and dissemination with the concomitant use of immunosuppressive agents such as oral corticosteroids, cyclosporine, azathioprine.

Prophylactic use of anti-viral agents (acyclovir, valacyclovir) in those patients who have an established history of HSV infection with severe and recurrent outbreaks have been suggested by authors and recommended valacyclovir 500 mg twice daily for the prevention of HSV reactivation.[2] Furthermore, a prophylaxis with acyclovir 200 mg twice daily or valacyclovir 500 mg per day is also recommended in AD patients with a history of EH and recurrent episodes. In addition, the concomitant use of topical tacrolimus should be avoided in AD patients on JAK inhibitors to prevent induction of EH.[6]

It is prudent to discuss regarding the prevention of HZ, HSV reactivation and EH in AD patients on JAK inhibitors. The American College of Rheumatology (ACR) recommends vaccination for patients ≥50 years before treatment of biologics and tofacitinib.[7] The American College of Gastroenterology recently recommended vaccination against HZ in IBD patients ≥50 years of age, including immunosuppressed patients.[8] Therefore, it is suggested to start JAK inhibitor treatment at least 2–4 weeks after live attenuated zoster vaccine.[9] Early detection either clinically or serologically and prophylaxis with valacyclovir or acyclovir can prevent severe episodes of EH, HSV reactivation and dissemination. In a study by Fleming et al.[10] which included 8 randomized controlled trials with 2706 participants found a risk reduction of nearly 70% for EH in dupilumab treated AD patients.

JAK inhibitors have a wider pleiotropic biological effect than biologics as they are able to simultaneously suppress the action of different cytokines. This intrinsic characteristic of JAK inhibitors can explain the higher risk of HZ, induction of EH and HSV reactivation. During the literature search, JAK 2 and 3 are found to be associated with increased risk of zoster infection and selectively JAK1 inhibition with a lower risk. Therefore, it may be speculated that selective JAK 1 inhibitor in AD might pose a relatively lesser risk of HSV, HZ, and EH. Moreover, anti-viral prophylaxis and vaccination may also be considered for alleviating the risk of

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viral infections. However, further long-term clinical studies are required to validate the findings.

## Conflict of interests

The author declares they have no conflict of interest.

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