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JAK-STAT Pathway and Pemphigus: Emphasis on Therapeutic Opportunities

Introduction

Pemphigus Vulgaris (PV) is a rare, but serious disorder, characterized with erosive and bullous lesions on mucous membranes and skin and associated with debilitating quality of life [1]. Increased understanding of the pathogenesis of pemphigus is necessary to find novel treatments: Previous studies have shown an imbalance of Th1/Th2 response and predominant involvement of Th2 pathway in pemphigus [2]. However, other subsets, such as Th17 have been shown to play an important role as well [2].Tyrosine kinases of the Janus family (Janus kinases or JAKs) have been recently shown to have central role in the immune responses due to their association with many cytokine receptors [3]. The JAK-STAT (Signal Transducers and Activators of Transcription) pathways include four JAKs (JAK1–3 and tyrosine kinase 2, TYK2) and seven STATs (STAT1-5a/b, 6) in mammals and each cytokine impose its effect on cells throughout a specific JAK-STAT combination.

Contrary to JAK1, JAK2, and TYK2 which are expressed on many cells, JAK3 is predominantly expressed on hematopoietic cells with a wide range of impacts on B lymphocytes [4]. The study of immune-localization of the JAK/STAT pathway in different layers of epidermis suggests the importance of level of their expression for normal functioning of the epidermis [5]. Moreover, expression of the JAK-STAT signaling pathway in bullous pemphigoid [13] and role of JAK in the pathogenesis of PV has been recently reported [6]. Juczynska et al. suggested that JAK2 expression may be dependent on IL-5 and IFN-γ signaling, while JAK3 expression might relate to Th17 and IL-4 signaling [7]. They also reported the expression of JAK3, STAT2, STAT4 and STAT6 in pemphigus vulgaris [7]. A recent study confirmed the increased expression of JAK3, STAT4 and STAT6 (but not STAT2) in oral mucosa lesions of patients with PV in study groups in comparison to the control group.

Letter to the Editor

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Since JAK3 plays a role in the signaling of IL-2, it might be involved in the recurrence of lesions in the course of disease and also could be assumed as a marker for monitoring the activity of the PV. While STAT4 signaling initiated mainly by IL-12 and play a crucial role in differentiation of the Th1 cell line, STAT6 is mainly involved in Th2 cell response [8]. Increasing both STAT4 and STAT6 expression in oral lesions of patients with PV in this study might be related to the issue of Th1/Th2 imbalance in the etio-pathogenesis

of PV. A recent narrative review article suggested the effectiveness of JAK inhibitors in the treatment of many autoimmune bullous disorders including PV [9]. Tofacitinib, an inhibitor of JAK1, JAK3 and to a lesser extent JAK2, has been proposed as a potentially effective drug to treat pemphigus due to the essential role of IL-4 and IL-21 in the development of PV [10]. In 2022, Vander et al. reported a case of PV with nail involvement with a prominent clinical response to combination of rituximab and oral tofacitinib.

Since the onset of action of rituximab has been shown to be slow in pemphigus, the striking improvement in nail lesions of this case considered to be due to tofacitinib [11]. One can infer that combining tofacitinib with rituximab which has been shown to be a potent treatment of PV might add the advantage of rapid disease improvement to long-term remission potential of rituximab. Surprisingly, a very recent study reported an increase in incidence of PV in patients receiving tofacitinib for different disorders including rheumatoid arthritis, psoriatic arthritis, ulcerative colitis, polyarticular course juvenile idiopathic arthritis, and ankylosing spondylitis according to the FDA Adverse Event Reporting System (FAERS) database. They reported some predisposing factors including female gender, age between 40-49 and having been suffered from rheumatoid arthritis [12]. However, indefinite attribution of events to the drug along with incomplete reports on FAERS, make it hard to rely on their findings.

Moreover, while tofacitinib was in the market since 2012, more than 90% of medication-related PV cases were reported in the past 2 years. Considering the fact that incidence of many immune-mediated disorders including PV has been risen recently in COVID-19 era due to both viral infection and its vaccination [13-15], attributing the newly diagnosed PV merely to tofacitinib administration seems hard and need further investigations. Oclacitinib is a selective JAKi which has been successfully used in some cases of blistering disorders such as pemphigus foliaceus and subepidermal blistering dermatosis in animals [16-17]. Ruxolitinib, another inhibitor of JAK1 and JAK2 pathways, might be the potential treatment of BP and DH on the basis of its ability to suppression of Th17 cell differentiation, which is critical in both dermatoses [18]. Small structure of JAK inhibitors and their acceptable bioavailability let us using them in both oral and topical forms which could be considered as a superiority over rituximab regarding the avoidance of venipuncture and hospitalization and superior patient convenience.

Moreover, the presence of ectopic lesional lymphoid population might mandate the use of topical potent treatments such as topical form of JAK inhibitors in some patients especially those with relapse following rituximab therapy. On the other hand, targeting both T and B cells by JAKis could be another strength of this class of medications over rituximab. Another interesting point of view is about different cytokine profiles during pemphigus phases which might affect choosing the appropriate medication regarding the dominant cytokine profile. Actually, switching between the immune responses' arms in early versus late phases of the disease as well as the previous exposure to certain medications might explain different characteristics of various phases of disease and affect the therapeutic response of different medications including rituximab. It has been shown that clinical outcome and safety profile of rituximab is different between patients treated early or late in the course of disease [19-20].

Hence, using new generation of JAKis with more specific targets might be of a great importance in inducing remission in various phases of disease. The comparison of particular JAK/STAT expressions and cytokine levels in serum and lesional tissue as well as investigating their correlation with different clinical characteristics such as PDAI or location of lesions could be interesting perspectives in this regard and help to find more specific medications and the best route of administration of them in each patient because considering its high heterogeneity, this disorder could not be managed with a one-size-fits-all approach. The results of future studies in this regard are eagerly awaited due to their important effects on altering treatment paradigms through better clinical efficacy along with fewer side effects in pemphigus patients with the view of personalized medicine.

Conflicts of interest

The authors have no conflicts of interest to declare that are relevant to the content of this article.

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Author's contribution

P.H, H.N, A.K and Z.A. performed the research. P.H designed the research study and supervised the findings of this work. All authors discussed the results. A.K wrote the initial draft. H.N and Z.A wrote the revised version.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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