Hidradenitis Suppurativa and JAK Inhibitors

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Contributor: Fabrizio Martora , Massimiliano Scalvenzi , Angelo Ruggiero , Luca Potestio , Teresa Battista , Matteo Megna

Hidradenitis suppurativa (HS), also known as acne inversa or Verneuil's disease, is a chronic, inflammatory, recurrent, and debilitating skin disease of the hair follicles characterized by inflammatory, painful, deep-rooted lesions in the areas of the body characterized by the presence of the apocrine glands. Unfortunately, huge unmet needs still remain for its treatment. More evidence is present thanks to the use of Janus kinase (JAK) inhibitors. Inhibition of Janus JAK 1 signaling in HS has shown clinical efficacy only at the highest dosages.

hidradenitis suppurativa JAK inhibitors treatment pathogenesis

1. Introduction

Hidradenitis suppurativa (HS), also known as acne inversa or Verneuil's disease, is a chronic, inflammatory, recurrent, and debilitating skin disease of the hair follicles that usually presents after puberty with inflammatory, painful, deep-rooted lesions in the areas of the body characterized by the presence of the apocrine glands: the armpits, breast, groin, gluteal area, and perianal area [1][2]. HS is now considered as a pathology of the pilosebaceous follicle unit [3].

The treatment of HS has always been a real challenge for dermatologists; mild HS forms are usually treated with conservative treatment such as topical resorcinol or clindamycin or hair laser epilation while moderate to severe forms undergo long-term antibiotics or may be candidates for biological therapies [4][5][6][7][8][9][10]. To date, the only biologic drug approved for HS is adalimumab, an anti-tumor necrosis factor (TNF)-α drug [11][12][13].

However, the efficacy of adalimumab in daily practice is highly variable [14][15], and the need to identify new therapeutic targets for patients with HS still remains a significant unmet need.

To date, there are ongoing phase III or phase II studies in the literature with anti-interleukin (IL)-17 drugs bimekizumab and secukinumab [16][17][18] Particularly, secukinumab is the biologic drug in the most advanced stage of clinical development for HS, showing promising results [16]. The role of IL-23 is still very controversial; indeed, to date, the only published phase II study involves the use of risankizumab at doses of 180 mg or 360 mg, which showed no difference: primary endpoint (HiSCR) was achieved by 46.8% of patients with risankizumab 180 mg, and 43.4% with risankizumab 360 mg [19]. Data on the clinical trial involving another anti-IL23, guselkumab, have not yet been published (ClinicalTrials.gov identifier: NCT03628924).

With regard to other biologics, there is still very little evidence in the literature on the treatment of HS targeting IL 36 (spesolimab). In this case, the activation of neutrophils could favor the outcome of the treatment because it adapts to the pathogenesis of HS; the results of the spesolimab study are awaited from the phase II trial [18].

More evidence is present thanks to the use of Janus kinase (JAK) inhibitors. Inhibition of Janus JAK 1 signaling in HS has shown clinical efficacy only at the highest dosages, highlighting that careful surveillance of the balance between the safety and efficacy of JAK inhibition is warranted [19].

These drugs act on JAKs, a family of four proteins: JAK1, JAK2, JAK3, and TYK2 [20]. Thanks to the activation of intracytoplasmic transcription factors such as signal transducer and transcription activation (STAT), they manage to modulate the inflammatory process [20].

Consequently, after activation, they move into the nucleus forming dimers, positively or negatively modulating thousands of genes [21].

The administration of these drugs involves both the oral and topical route, therefore, their use in various chronic inflammatory diseases including HS was immediately of great interest to dermatologists [22][23].

2. Hidradenitis Suppurativa and JAK Inhibitors

HS is a chronic inflammatory disease that occurs in regions where there is a greater presence of apocrine glands [24]. The primum movens of the pathology is the occlusion of the follicular ducts, leading to the formation of nodules, abscesses, and fistulous tracts, which may cause local superinfections [24].

The first line of treatment for mild HS involves the use of antibiotics, anti-inflammatory, corticosteroids, and hair laser epilation [25][26]. Moderate to severe forms may be eligible for biological therapies.

Surgical treatment for HS is a valid alternative to the treatments mentioned; several cases have been reported in the literature that show good therapeutic results with this technique [27][28].

To date, thanks to recent studies, we are moving toward the role of cytokines in HS [28][29][30][31]; it has been clarified that there is an overexpression of IL-17A, IL-26, IFN-γ, IL-27, and IL-β and a concomitant downregulation of IL-22 in the lesions of HS patients [29][30]. Adalimumab, an anti-TNF agent, remains the only biologic drug approved for HS [31], with an efficacy rate reaching an approximately 60–70% mean efficacy rate in real-life [14].

During these years, there have been various studies where drugs targeting IL1, IL17, and IL23 cytokines have been tested [32]. The most promising results from real-life would seem to direct us toward the use of secukinumab, an anti-IL17A, which reports a mean efficacy rate of about 60% [14].

As stated above, pro-inflammatory cytokines are crucial for HS development so inhibition of the JAK/STAT pathway could help to regulate the expression of inflammatory factors such as IL-6 or IL-23 simultaneously [33][34][35][36][37].

Jak3 upregulation was found in the lesional tissue of HS patients [37]. The role of the JAK-STAT pathways in the regulation of cytokines, particularly type 1 cytokine receptors: ILs including IL-12 and IL-23 and type 2 cytokine receptors including IFN and IL-10-related cytokines [IL-10, IL-19, IL-20, IL-22, IL-26] could warrant a new therapeutic target for HS patients [37].

Unfortunately, there is no real resolutive therapy for HS due to the complexity of the pathogenesis, which is not yet well-defined; the efficacy results of the available treatments underline how necessary it is in the future to find new therapeutic targets.

In conclusion, in recent years, the interest in HS has strongly increased. To date, the only biological drug currently approved for HS is adalimumab. However, due to the chronic remitting course of the disease, there is still a huge unmet need for HS treatment.

Thanks to new studies, we are moving toward new classes of drugs against new immunological targets (IL-12, IL-17, IL-23, IL-36, CD-40, JAK family members, complement, LTA4 and CXCR1/2) that are under study [34][35][36].

There are still little data to understand the effectiveness of JAK inhibitors for HS. Particularly, there is only one published clinical trial in the literature (Janus kinase 1 inhibitor INCB054707), a real-life study with 15 patients up to week 24 with upadacitinib and a case series where tofacitinib was successfully used. Conversely, there are several ongoing clinical trials. The limited available data show promising results in terms of efficacy and safety. Hence, new studies are highly needed to test the validity of these new potential drugs for HS.

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