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Has the time come to assess small molecule/biologic drug combination for the management of moderate-to-severe hidradenitis suppurativa?

As the landscape for hidradenitis suppurativa (HS) medical treatment is rapidly expanding, seemingly going over the same steps that marked the evolution of psoriasis management, upcoming agents still do not appear to offer complete disease control, in many cases. Both International HS Severity Score System (IHS4)-55 and HS Clinical Response (HiSCR)50 initial response rates have not substantially increased since the publication of adalimumab landmark trials, ranging between 40-60% for upcoming biologics like the anti-interleukin(IL)-17A secukinumab[1] and anti-IL17A/F bimekizumab.[2] Moreover, such outcome measures do not reach close to the disease response level (e.g., Psoriasis Area and Severity Index 90) now accepted in psoriasis. Higher figures have been reported only in the JAK1 inhibitor povorcitinib phase II open label extension and in small studies with off-label brodalumab, an anti-IL17-RA agent, and upadacitinib, another JAK1 inhibitor.[2] Although the latter phase II trials provide only signals of response rates, rather than precise effect sizes obtained through the completion of phase III studies, they cannot be easily disregarded.

Since both JAK inhibitors and anti-IL17 agents would appear to be highly effective in HS, it is thought-provoking that they exploit different, only partially overlapping steps in HS pathophysiology.

Indeed, among pivotal interleukins involved in HS pathogenesis, IL17, which is known to have a role in advanced, high inflammatory burden lesions, is the only one that does not signal through the JAK/STAT pathway. Conversely, JAK1 is involved in important steps in the initiation of the inflammatory process. Indeed, hair follicle stem cells isolated from HS patients exhibit signs of replication stress that result in an IFI16/STING-dependent production of type I interferons. The latter signal through the JAK1/STAT1 pathway, presumably setting HS pathogenesis in motion. It must be emphasized that a multitude of other disease-relevant cytokines act via this pathway later in HS pathogenesis, which is in keeping with aforementioned clinical evidence and with the findings of a recent transcriptomic study.[3] As HS progresses, a number of cells (i.e., neutrophils, macrophages, B cells and fibroblasts) and effector molecules (TNFα, IL17, IL23, C5a etc.) come into play, likely generating a transcriptional noise that overshadows such early events (**Fig. 1**).[4]

Similarly, from a clinical perspective a duality also appears to exist in HS course, with a pauci-inflammatory phase followed (in a proportion of cases that is probably defined by the individual's genetics) by an intensely inflammatory one, which then self-perpetuates and produces irreversible scarring.[4]

With new agents promising to selectively target different elements of HS immunopathogenesis, it may be possible to combine drugs that exclusively block B cells or fibroblasts, with those targeting IL17-dependent inflammation. In future combining small molecule/biologic drugs could be regarded similarly to combining biologics with antibiotics and/or surgery nowadays.

To date, only a case report exists on small molecule/biologic drug combination. Agud-Dios *et al.* documented an excellent response of both HS and concomitant Crohn's disease with guselkumab plus apremilast, where multiple biologics had previously failed.[5]

Ideally, in future we should aim to identify HS patients at high risk of rapid progression and focus combination treatment on these patients where needed to gain rapid disease control and prevent irreversible scarring.

Considering currently available evidence, the combination of upadacitinib or povorcitinib plus an anti-IL17 such as secukinumab, bimekizumab, or brodalumab, possibly frequency-intensified, may hypothetically address most key events in HS pathogenesis. From a pharmacoeconomic perspective, high-dose anti-TNFα agents (such as infliximab or adalimumab biosimilars) plus JAK1 inhibitor would also make a compelling case (**Tab. 1**). Understandably, safety of small molecule/biologic drug combinations will be a priority concern. Excessive immunosuppression might expose patients to the risk of infectious complications. However, there is persistent inflammation (i.e., undertreatment) in severe HS cases and a relative paucity of superinfections in this setting. While safety signals from the ORAL Surveillance trial on tofacitinib, a pan-JAK inhibitor, prompted regulators to extend boxed warnings to other JAK inhibitors, analysis of phase III trials on upadacitinib in rheumatoid arthritis revealed similar rates of major cardiovascular events (MACE) and venous thromboembolism relative to placebo and reference comparators, with no increase over time.[6] From a practical perspective, careful patient selection and appropriate dose tailoring of JAKi will be important given the increased background risk of thromboembolic events and MACE in HS patients.[7]

While phase III data on JAK inhibitors are needed to adequately gauge their true efficacy and safety profile in the first instance, better control of severe HS cases refractory to biologic monotherapy may require investigation of small molecule/biologic drug combinations sooner rather than later.

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