Itch-directed therapeutics in hidradenitis suppurativa: a mechanism-based synthesis of an emerging but fragmented evidence base

Category: Therapeutics

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Abstract

Pruritus is a common and clinically significant symptom of hidradenitis suppurativa (HS), independently associated with impaired quality of life, yet it remains chronically underassessed relative to other core outcomes [1,2]. Despite growing recognition of itch as a distinct treatment target, no existing synthesis organizes the fragmented itch-directed therapeutic evidence in HS by mechanism of action, and few therapies have been rigorously studied for this indication specifically [6]. This review addresses that gap through a mechanism-based synthesis spanning HS pathophysiology and pharmacologic evidence across five itch-relevant pathways: Janus kinase (JAK)-STAT signaling, interleukin (IL)-17/23, IL-4/13 (Th2), IL-31/neuroimmune signaling, and opioid receptor modulation. Pathophysiologically, itch in HS reflects overlapping peripheral sensitization and central neuroendocrine-immune crosstalk [8], but HS is comparatively less Type 2-skewed than atopic dermatitis or psoriasis, a critical caveat when

extrapolating Th2-pathway rationale to HS-associated itch [3]. Evidence synthesis reveals a striking asymmetry: JAK1 inhibition carries the strongest itch-specific signal to date, with a phase 2 randomized controlled trial of povorcitinib explicitly capturing itch as a patient-reported outcome [4], corroborated by phase 3 povorcitinib data [10]. Approved IL-17/23 biologics (adalimumab, secukinumab, bimekizumab) [9] demonstrate disease-activity control with itch captured through validated symptom diaries in pooled bimekizumab data [7]. However, IL-4/13 (dupilumab) evidence remains limited to case-level reports including at least one documented treatment failure consistent with HS's comparatively limited Type 2 polarization [5]. By contrast, IL-31-pathway agents and antihistamines represent complete evidence gaps in HS-specific itch despite routine off-label antihistamine use in clinical practice. Building on this synthesis, we propose a phenotype-based mechanism-to-treatment algorithm (Figure 1) that stratifies patients by disease-activity status and itch persistence to guide escalation from approved biologics to JAK1 inhibition to itch-targeted neuromodulation. This review is, to our knowledge, the first to organize itch-directed HS therapeutics by mechanistic pathway rather than by drug class alone, translating a fragmented and heterogeneous evidence base into an actionable clinical framework while explicitly naming the evidence gaps — IL-31 blockade, antihistamines, and itch as a prespecified randomized endpoint — that must be closed to advance the field. As itch prevalence and burden in HS rival those of pain yet remain comparatively understudied and undertreated, this synthesis offers clinicians and investigators a roadmap for evidence-based itch management and a prioritized future research agenda.

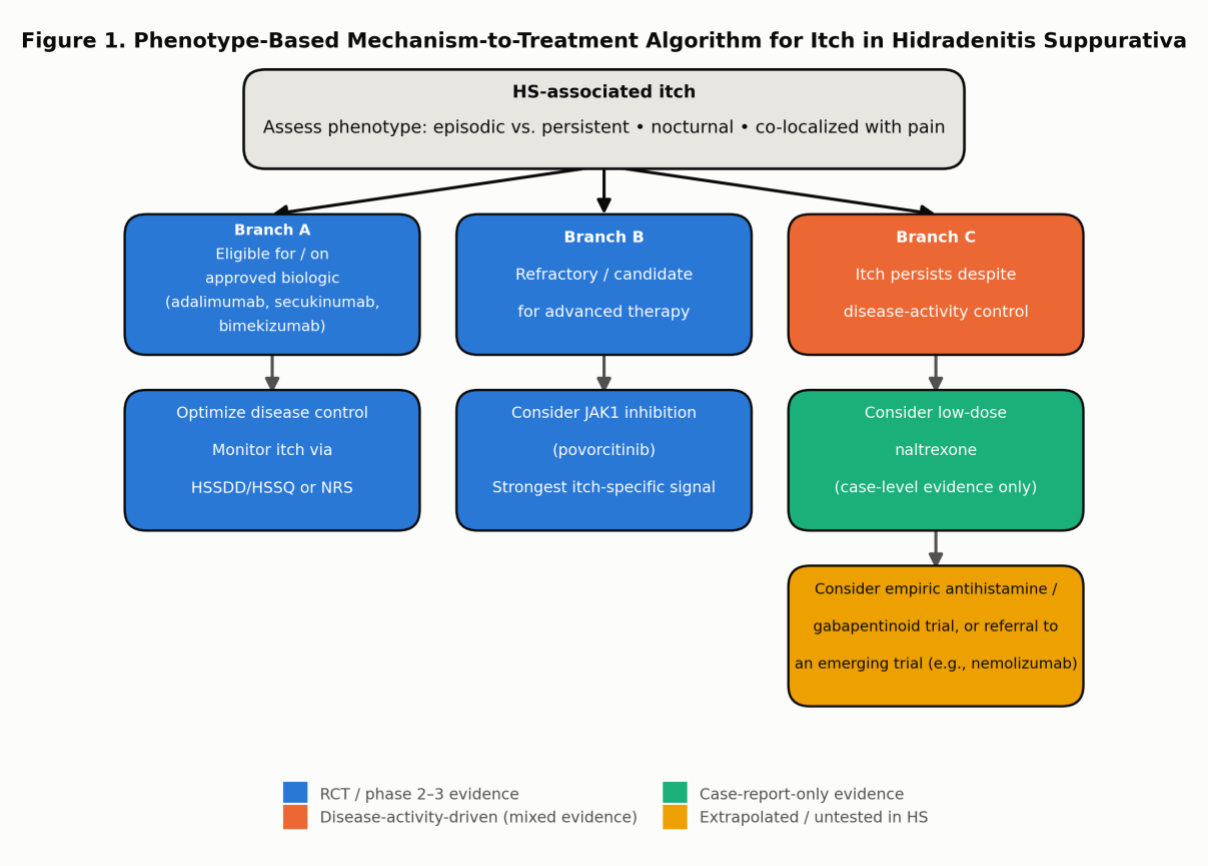


Figure 1. Phenotype-based mechanism-to-treatment algorithm for itch in hidradenitis suppurativa.

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