VOLUME - 15, ISSUE - 09, SEPTEMBER - 2026 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Medical Science

NAVIGATING THE NEW BIOLOGIC ERA IN HIDRADENITIS SUPPURATIVA: EMERGING MOLECULAR TARGETS, BIOMARKERS, AND UPDATED TREATMENT

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ABSTRACT Hidradenitis suppurativa is a debilitating chronic inflammatory disease characterized by painful nodules, abscesses, and progressive sinus tract formation. For decades, empirical antibiotic regimens dominated clinical practice without addressing the underlying immune dysregulation. Recent breakthroughs in translational immunology have identified key cytokine drivers, shifting the paradigm toward targeted biological therapies. This review examines the follicular immune cascades involving the IL-23/IL-17 axis, TNF-alpha, and neutrophil recruiting pathways that propagate tissue destruction. We summarize evidence for approved biologic agents, notably adalimumab and secukinumab, while evaluating emerging therapeutic candidates including dual IL-17A/F inhibitors, oral JAK1 inhibitors, and complement pathway modulators.

KEYWORDS : Hidradenitis suppurativa, Biologics, Interleukin-17, Adalimumab, Biomarkers

INTRODUCTION

Hidradenitis suppurativa represents one of the most clinically challenging and psychosocially devastating chronic inflammatory skin disorders encountered in modern dermatology (1). Characterized by recurrent, painful, deep-seated inflammatory nodules, sterile abscesses, draining fistulae, and extensive dermal fibrosis, the condition primarily affects intertriginous anatomical regions, including axillary, inguinal, perianal, and inframammary folds (1). Beyond the profound physical disfigurement and unremitting pain, affected individuals bear an immense psychosocial burden characterized by alarmingly elevated rates of clinical depression, social isolation, work impairment, and suicidal ideation compared to cohorts with other chronic dermatologic diseases (2,3).

METHODS

A rigorous literature retrieval was designed across four electronic citation engines: PubMed, Scopus, Embase, and Google Scholar. The query strategy incorporated medical subject headings and controlled keywords, including hidradenitis suppurativa, acne inversa, biologic agents, interleukin inhi-bitors, Janus kinase inhibitors, biomarkers, and clinical trials. Following qualitative assessment, 15 relevant publications were included in the final qualitative narrative synthesis to elucidate inflammatory networks, clinical trial findings, and personalized algorithmic paradigms in hidradenitis suppurativa (Figure 1).

Molecular Pathophysiology and Cytokine Signaling Networks

The immunopathogenesis of hidradenitis suppurativa is rooted in hyperkeratosis of the follicular infundibulum followed by occlusion, dilatation, and catastrophic mechanical rupture of the terminal pilosebaceous unit (3). Follicular rupture releases commensal microbial patterns, cellular debris, and damage associated molecular patterns directly into the surrounding sterile dermis (3). This event provokes instant activation of resident dendritic cells and dermal macrophages via Toll-like receptors, triggering downstream nuclear factor kappa-light-chain-enhancer of activated B cells signaling and assembly of the NLRP3 inflammasome complex (4). Proteolytic cleavage of procaspase-1 subsequently drives high-level maturation and secretion of interleukin-1beta and interleukin-18, establishing a potent pro-inflammatory cytokine microenvironment (4). Simultaneously, hyperactive macrophages release substantial quantities of tumor necrosis factor alpha, which enhances vascular permeability, upregulates endothelial adhesion mole-cules, and amplifies local tissue necrosis (4). Dermal dendritic cells primed by danger signals produce high titers of inter-leukin-23, which directs naive CD4 positive T helper cells and innate-like lymphocytes toward a robust type 17 effector program (5). Secretion of interleukin-17A, interleukin-17F, and interleukin-22 from polarized cells stimulates neighboring keratinocytes and dermal fibroblasts to express elevated concentrations of chemokines such as CXCL1, CXCL2, and CXCL8 (5).

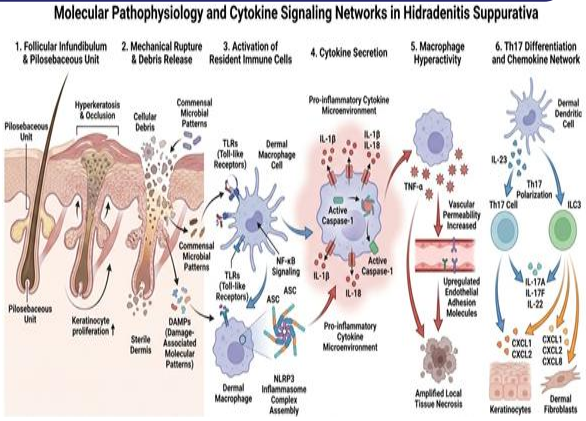

Figure 2. Molecular Pathophysiology.
Source: author.

Established and Approved Biologic Therapies (Anti-TNF and Anti-IL-17A)

The therapeutic landscape underwent an initial paradigm shift with the approval of adalimumab, a fully human monoclonal IgG1 antibody specifically targeting soluble and membrane-bound tumor necrosis factor alpha (6). Landmark pivotal phase III clinical trials, PIONEER I and PIONEER II, demonstrated that weekly administration of 40 mg adalimumab achieved statistically significant improvements in the validated hidradenitis suppurativa clinical response endpoint at week 12 compared to placebo (6). Sustained open-label extension studies confirmed meaningful redu-ctions in painful inflammatory nodules and abscesses alongside improvements in systemic inflammatory parameters (6). However, long-term registry data demonstrate that a considerable proportion of treated patients experience primary non-response or develop secondary loss of response, often mediated by immunogenicity and neutralizing anti-drug antibody generation (7). Furthermore, tumor necrosis factor blockade frequently fails to arrest active epithelial sinus tract suppuration or clear deep-seated cicatricial tunnels, exposing clear mechanistic limitations in single-pathway blockade (7). More recently, secukinumab, a selective human monoclonal antibody targeting interleukin-17A, secured regulatory approval based on robust outcomes from the parallel phase III SUNSHINE and SUNRISE programs (8). Patients receiving secukinumab every two weeks demonstrated rapid and sustained improvements in clinical response through 52 weeks, with significant reductions in inflammatory nodule count and minimal skin-related adverse reactions (8). These findings established interleukin-17A blockade as an efficacious, safe first-line biological alternative, validating the pivotal role of the Th17 cytokine pathway in controlling continuous follicular inflammation (8).

Emerging Molecular Targets and Investigational Pathways

To overcome incomplete disease control achieved by monovalent cytokine blockade, translational drug development has expanded into novel downstream targets and intracellular signaling cascades (9). Bimekizumab, a humanized monoclonal IgG1 antibody engineered to selectively neutralize both interleukin-17A and interleukin-17F, has emerged as a promising biologic in phase III clinical evaluation (9). Because interleukin-17F cooperates synergistically with interleukin-17A to stimulate inflammatory chemokine expression from stromal fibroblasts and keratinocytes, dual inhibition achieves deeper and more rapid clinical responses in both nodular and fistulizing disease (9). Parallel attention has focused on intracellular signaling inhibition through small oral molecules, particularly selective Janus kinase inhibitors (10). Agents such as povorcitinib, an oral Janus kinase 1 inhibitor, block signaling downstream of diverse cytokine receptors, simultaneously interrupting the biological activity of interleukin-6, interferon-gamma, and common gamma chain cytokines (10). Phase II trials have revealed rapid reductions in pain scores and inflammatory drainage among individuals refractory to previous biological agents (10). Furthermore, activation of the complement cascade, notably the generation of potent anaphylatoxin C5a, has been recognized as an essential driver of neutrophil priming and tissue destruction (11). Interventions directed against the C5a receptor or inhibiting terminal complement components aim to quell neutrophil -mediated oxidative bursts and dermal necrosis (11). Finally, therapeutic blockade of the interleukin-1 family, including interleukin-1 receptor antagonists and anti-interleukin-36 receptor monoclonal antibodies, represents an active domain intended to silence upstream innate autoinflammatory cascades within the follicular unit (11).

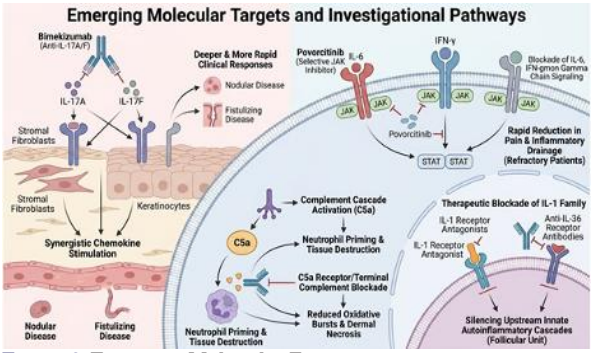

Figure 3. Emerging Molecular Targets.
Source: author.

Circulating, Tissue, and Imaging Biomarkers for Precision Stratification

Optimizing biologic intervention requires objective biological readouts capable of predicting disease velocity, aggressive destructive phenotypes, and individual therapeutic response (12). Classical systemic inflammatory markers, including high-sensitivity C-reactive protein and erythrocyte sedimen-tation rate, correlate moderately with aggregate lesion burden but lack discriminatory capacity to identify specific immunological subphenotypes (12). In contrast, compre-hensive multiplex serum profiling has identified distinct circulating biomarkers, such as elevated levels of interleukin-6, CXCL8, and matrix metalloproteinases 8 and 9, which correspond closely to high inflammatory burden and destruc-tive dermal matrix remodeling (12). Direct transcriptomic and proteomic profiling of cutaneous biopsy specimens highlights distinct patient subsets dominated either by an exaggerated type 17 inflammatory axis or an intensely autoinflammatory, neutrophil-rich interleukin-1/chemokine expression profile, suggesting a clear rationale for customized biologic selection (13). Alongside molecular analytes, high-frequency cuta-neous ultrasonography has emerged as a practical imaging modality for bedside phenotypic evaluation (13). Ultrasound assessment reliably visualizes subclinical fluid collections, determines exact dermal sinus tract depth and branching complexity, and tracks Doppler vascularity signals within inflammatory borders (13). Longitudinal reduction in Doppler signals and progressive regression of hypoechoic dermal tunnels provide early quantitative imaging metrics of biologic treatment response prior to visible macroscopic surface remodeling (13).

Contemporary and Updated Treatment Algorithms

Modern management frameworks demand a rapid progression toward phenotype-guided therapeutic sequencing, moving decisively past prolonged empirical antibiotic maintenance (14). Baseline stratification should incorporate both the anatomic Hurley staging system and dynamic scoring metrics, notably the International Hidradenitis Suppurativa Severity Score System, to gauge lesion activity and structural damage accurately (14). For patients presenting with moderate-to-severe disease characterized by multiple recurrent abscesses, inflammatory nodules, or early sinus tract initiation, biologic therapy should be instituted promptly as first-line disease-modifying treatment rather than reserved for late salvage (14). Adalimumab or secukinumab represents standard first-line biologic selection (14). Response must be evaluated formally at 12 to 16 weeks; if an adequate clinical reduction in inflammatory lesions is not achieved, early dose optimization or class-switching to dual interleukin-17A/F blockade or participation in clinical trials evaluating Janus kinase inhibitors should occur (14). Importantly, biologic administration must be synergistically coupled with timely procedural and surgical interventions (15). While biologic therapies effectively suppress active dermal inflammation, downregulate vascularity, and mitigate peri-lesional edema, they cannot resolve inert epithelialized sinus tracts and fibrous scar tissue (15).

Diagnostic Gaps, Clinical Trial Endpoints, and Future Perspectives

Despite therapeutic advances, significant clinical hurdles remain regarding diagnostic recognition and standardized outcome measures in clinical trials (14). The traditional hidradenitis suppurativa clinical response score, defined as a 50 percent reduction in inflammatory nodule and abscess count with no increase in either parameter, has served as a foundational regulatory endpoint (14). However, this benchmark fails to capture deep clinical responses, provides inadequate sensitivity to assess sinus tract drainage cessation, and overlooks progressive fibrosis (14). Stricter endpoints, including 75 percent, 90 percent, or complete resolution of inflammatory lesions, alongside validated fistula-specific scoring tools, are crucial to discern the true efficacy of next-generation therapies (14). Furthermore, hidradenitis suppurativa must be addressed as a systemic autoinflammatory disorder rather than an isolated cutaneous pathology (15). Systemic comorbidities, including metabolic syndrome, severe cardiovascular disease, axial spondyloarthritis, and inflammatory bowel disease, are frequent and require coordinated multidisciplinary management (15). Advancing precision medicine in this condition will necessitate integrating genetic profiling, serum cytokine signatures, and cutaneous ultrasound imaging into machine learning algorithms to match individual patients with ideal molecular targets, minimizing therapeutic trial-and -error and preventing irreversible physical and psychological disability (15).

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