Concurrent Anticytokine Biologics for the Management of Severe Hidradenitis Suppurativa: Are They Safe and Effective?

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Dysregulated immune responses including elevations in the inflammatory cytokines tumor necrosis factor (TNF),[1-4] IL-1β,[3] and IL-12/23[5-7] have been identified in hidradenitis suppurativa (HS). Targeted biologic agents may offer an opportunity to intervene in specific aberrant inflammatory pathways to effectively treat HS while minimizing adverse effects (AEs). There is growing evidence, however, that treatment of HS with a single biologic agent is not effective in all patients.[6,8-17] The TNF antagonist adalimumab has been shown to achieve clinical response in approximately 50% of patients (N=633).[18] In smaller and uncontrolled studies, clinical response was achieved in 70% (7/10) of patients treated with the IL-1 antagonist anakinra[16] and 47% (8/17) of patients treated with the IL-12/23 antagonist ustekinumab[19]; however, larger rigorous studies are needed. There is an urgent need for more effective therapeutic strategies for this condition.[20]

The administration of concurrent biologics may offer the potential for improved disease control through synergistic targeting of multiple inflammatory pathways, particularly for severe and recalcitrant HS. This approach may be effective given insights from mechanistic studies suggesting the involvement of multiple inflammatory pathways in the disease pathogenesis.[3,21] Concurrent anticytokine biologics have been used safely and effectively in other inflammatory diseases; for example, combination therapy with TNF and IL-12/23 antagonists have resulted in near-complete to complete resolution of severe psoriatic skin and joint disease without AEs.[22-24]

An increased risk for infection without increased efficacy associated with the use of concurrent anticytokine biologics for treatment of rheumatoid arthritis (RA) has raised concerns about the safety of this therapeutic approach. In a study of concurrent etanercept and anakinra therapy for RA (N=244), the combined therapy was not more efficacious than etanercept alone (American College of Rheumatology 50% response at week 24: etanercept 25 mg twice weekly, 41%; etanercept 25 mg twice weekly plus anakinra 100 mg once daily, 31%; etanercept 25 mg once weekly plus anakinra 100 mg once daily, 39% [*P*=.914]).[25] Combination therapy also was associated with a higher overall incidence of serious AEs, serious infections requiring antibiotics or hospitalizations, and serious infections leading to study withdrawal. Reported infections included pneumonia, cellulitis, herpes zoster, pneumonitis, and pyelonephritis, but no opportunistic infections or tuberculosis were reported. A single case of lymphoma was reported in the full-dose etanercept plus anakinra group; however, the association with therapy is unclear, as RA itself is associated with an increased risk of malignancy.[25]

Although these results are notable, caution must be exercised in extrapolating safety and efficacy data for treatment with concurrent biologics from the RA literature for management of HS for several reasons. First, RA is an autoimmune disease that is associated with an increased risk for genitourinary and bronchopulmonary infections and septic arthritis, even in the absence of treatment with steroids and immunomodulatory drugs.[26,27] Increased risk for development of lymphoma, lung cancer, and nonmelanoma skin cancer also has been associated with RA.[28,29] The exact etiology of this increased risk is unknown, but it is thought to relate to immunologic disturbances and chronic systemic inflammation associated with RA.[29] Furthermore, RA disease characteristics and comorbidities that may contribute to an increased risk for infection and malignancy include advanced age as well as a history of leukopenia, chronic lung disease, diabetes mellitus, alcoholism, and/or

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smoking.[30] Infection and malignancy risk in RA also may be compounded by immunomodulatory therapies.[31,32]

Conversely, although microbes are believed to play an important role in HS initiation and progression, HS is neither considered an infectious disease nor associated with an increased risk for infection.[33] Increased malignancy risk generally is not reported with HS, and systematic therapeutic trials of biologic therapies for HS have been notable for an absence of infectious or malignant AEs compared to placebo.[12,14,16,18,19] From a mechanistic standpoint, data suggest that HS may be fundamentally distinct from RA and other autoimmune diseases; therefore, it may not be appropriate to extrapolate safety data from the latter to guide therapeutic strategies for the former.

The concept that different inflammatory diseases harbor distinct risks for comorbidities and AEs associated with medications is further supported by data from patients with PAPA syndrome (pyogenic arthritis, pyoderma gangrenosum, and acne), a monogenic autoinflammatory disease characterized by inflammasome activation and subsequent increased signaling via IL-1.[34] Patients with PAPA syndrome often require a combination therapeutic regimen including simultaneous antibiotics, systemic retinoids and steroids, disease-modifying antirheumatic drugs, and more than 1 concurrent anticytokine biologic to manage their condition. Despite management with multiple immunosuppressants and immunomodulators, patients with PAPA syndrome rarely develop localized or systemic infections, supporting our hypothesis that different systemic immune-mediated disorders may render a distinct susceptibility to infectious complications. Clinically, patients with PAPA syndrome can have cutaneous disease manifestations consistent with HS, suggesting the possibility of shared underlying inflammatory mechanisms due at least partially to inflammasome activation. This clinical observation may help explain why concurrent anticytokine biologic therapies in conjunction with combinations of steroids and other immunomodulators may be safe and effective in HS patients.

We have safely and effectively treated 2 patients with severe HS with extended courses of concurrent TNF and IL-1 antagonists. Both patients had previously failed treatment with multiple therapeutic interventions, including topical and systemic antibiotics, disease-modifying antirheumatic drugs, hormonal therapy, biologic monotherapy with several targeted agents, and wide local excision. In the setting of concurrent certolizumab plus anakinra in the first patient and adalimumab plus anakinra in the second, both patients reported reduced drainage, pain, and number of disease flares. Both patients also were maintained on extended treatment courses (11 months and 2 years, respectively) without evidence of infection or malignancy.

Concurrent biologics may be safe and effective in managing recalcitrant HS; however, large prospective studies are needed to confirm these anecdotal findings. As our understanding of HS pathogenesis expands, novel and more effective therapeutic options will be developed. Until then, concurrent biologics may be a potential option for patients with severe recalcitrant HS.

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