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The Contradictory Inefficacy of Methotrexate in Hidradenitis Suppurativa: A Need to Revise Pathogenesis or Acknowledge Disease Heterogeneity?

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Abstract

The pathogenesis of Hidradenitis Suppurativa (HS) centers around Th17/Treg dysfunction illustrated by lesional elevation of IL-17A, IL-6, and other inflammatory mediators resulting in a chronic feed-forward inflammatory cascade. Similar inflammatory mechanisms have been identified in psoriasis and rheumatoid arthritis (RA) in which traditional immunosuppressants (including methotrexate) are routinely used with reasonable levels of disease control. Methotrexate's mechanism of action in these instances include downregulation of the Th17 axis via alterations in dendritic cell and T-cell activity and maturation. Published data suggests methotrexate in an ineffective therapy in HS, which does not pair with our current understanding of the mechanisms of disease. The reasons behind this, including are discussed. Some HS patients may benefit from drugs such as methotrexate, and acknowledgement of the potential of disease heterogeneity will allow exploration of which factors may enable identification of such individuals.

Keywords

Hidradenitis Suppurativa; Acne Inversa; Methotrexate; Th17; Efficacy; Pathogenesis

The pathogenesis of Hidradenitis Suppurativa (HS) centers around Th17/Treg dysfunction illustrated by lesional elevation of IL-17A, IL-6, and other inflammatory mediators resulting in a chronic feed-forward inflammatory cascade in the setting of follicular occlusion[1]. Similar inflammatory mechanisms have been identified in psoriasis and rheumatoid arthritis (RA) in which traditional immunosuppressants (including methotrexate) are routinely used with reasonable levels of disease control[2,3]. Methotrexate's mechanism of action in these instances include downregulation of the Th17 axis via alterations in dendritic cell and T-cell activity and maturation[4].

Since the FDA approval of Adalimumab for Hidradenitis Suppurativa in 2015, interest in the use of traditional immunosuppressant in HS has significantly decreased. Methotrexate, cyclosporine and dapsone are reported in HS with varying degrees of efficacy (Figure 1)[5].

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Taking into account the significant rates of placebo effects in HS clinical trials (up to 30% patients achieving HiSCR on placebo alone[6]) further question the true efficacy of these drugs. When traditional immunosuppressive agents are utilized, publication bias results in only isolated case reports of successful treatment, suggesting that broadly speaking, traditional immunosuppressants have poor efficacy in HS (Figure 1). This lack of efficacy does not pair with our current understanding of the mechanisms of disease[1].

Despite the decreased interest in the routine treatment of HS with such immunosuppressants, their utility should not be completely discarded. The fact that methotrexate has no evidence for clinical efficacy in HS leads to two possible conclusions: either that our pathogenic model of HS requires revision, or the existing data is prone to selection bias. In RA, methotrexate resistant disease is associated with longer disease duration, female gender, and increased levels of monocytes and neutrophils[3]. Anecdotally, these factors may be present in patients with ‘typical’ (axillary-mammary or LC1) HS. This also correlates with reports of ‘syndromic’ HS (associated with SAPHO or PASH syndrome) benefiting from methotrexate administration[7], and the fact that the studies of methotrexate in HS patients involved severe, Hurley stage 3 ‘treatment resistant’ patients[8].

Currently, investigations into HS (clinical, serological, microbiological, transcriptomic and genetic) consider HS as a homogenous disease. Such underlying assumptions may preclude identification of low-concentration or low-frequency markers important in pathogenesis, predictive of disease activity and/or treatment in specific subsets of HS patients. Preliminary data demonstrates differences in inflammatory cytokines in inflamed versus fibrotic HS lesional tissue[9]; and in other inflammatory skin diseases such as scleroderma, hierarchal clustering of transcriptomic data by clinical phenotype has provided valuable insights into differential activity of various mechanistic pathways in this disease. A similar approach would provide valuable insights in HS. Sufficient evidence exists to support the role of Th17/Treg axis in the inflammatory mechanisms of HS[1,9], but not necessarily in all presentations and in all stages of disease, and certainly not the sole pathogenic pathway. It follows, therefore, that the role of traditional immunosuppressants in HS has not yet been satisfactorily settled. Some HS patients may benefit from drugs such as methotrexate, and acknowledgement of the potential of disease heterogeneity will allow exploration of which factors may enable identification of such individuals.

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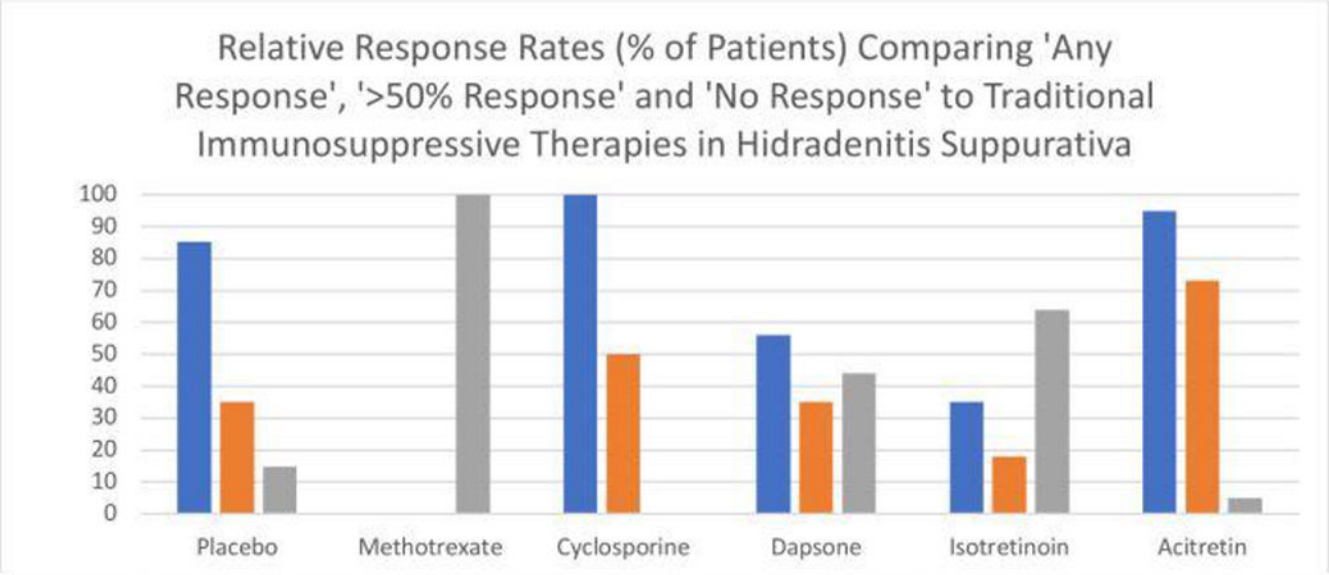

N=	163	3	4	34	174	22
Hurley 1	0%	0%	0%	35%	24%	12%
Hurley 2	54.6%	0%	25%	50%	55%	45%
Hurley 3	45.4%	100%	75%	15%	31%	43%

Figure 1:

Relative Efficacy of Systemic Immunosuppressants in Hidradenitis Suppurativa. Data adapted from Kimball et al[6] and Blok et al[5]. The corresponding table presents the number of patients exposed to each intervention, along with the subgrouping by Hurley stage. The external validity of the response data for each intervention is dependent upon the clinical presentation of the cohort (including severity of disease), known level of placebo effect and dosages administered.