Methotrexate shows benefit in a subset of patients with severe hidradenitis suppurativa

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Abstract

Background: Methotrexate is an immunomodulatory therapy that may offer benefit to patients with hidradenitis suppurativa (HS). Despite its theoretical advantages, there is a paucity of available data regarding long-term methotrexate use in patients with HS.

Objective: This study aimed to assess whether methotrexate treatment leads to improvement in HS disease severity.

Methods: We conducted an institutional review board–approved, single-center, retrospective chart review of patients with HS who were treated with methotrexate between 2000 and 2018. Primary outcome measurements included the HS Physician’s Global Assessment (HS PGA), Hurley staging, abscess count, fistula count, and inflammatory nodule count.

Results: A total of 29 patients were identified; 14 were excluded for reasons including never starting methotrexate and missing follow-up data. For remaining patients (n = 15), the average cumulative dose of methotrexate was 520.1 mg (range, 30–1665 mg) and the average length of treatment was 11.7 months (range, 1–38 months). Patients taking methotrexate as a primary therapy had a higher cumulative dose and length of treatment (520.13 mg; 14.6 months) compared with those taking biologics concomitantly (468.44 mg; 9.1 months). Patients using methotrexate as primary therapy demonstrated nonsignificant reductions in HS PGA, inflammatory nodule count, and abscess count. Patients on concomitant biologic therapy failed to demonstrate any change in HS PGA, inflammatory nodule count, and abscess count.

Limitations: Limitations of the study include its retrospective nature, small sample size, length of time on methotrexate between groups, and homogeneity of the patient population.

Conclusion: Methotrexate may represent an effective treatment option in older patients with lower body mass indices but fails to offer benefit in patients taking concurrent biologic therapy.

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Introduction

Hidradenitis suppurativa (HS) is a chronic, inflammatory skin disease that causes significant pain and morbidity. The disease is characterized by recurrent inflammatory nodules, abscesses, and fistula formation in the intertriginous areas of the body (Slade et al., 2003; Werth and Williams, 2000). The multifactorial pathophysiology of HS has led physicians to use many strategies in treatment, including hormonal medications, steroids, immunomodulatory therapies, and antibiotics in addition to surgical interventions (Saunte and Jemec, 2017). Despite this approach, patients commonly need to trial several therapeutic agents and/or use a combination of medications to obtain meaningful clinical improvement in HS.
In response to the complex etiology of the disease and the lack of reliable pharmacotherapy, some groups have investigated more nontraditional therapies, including nutritional interventions such as the Mediterranean diet (Barrera et al. 2019) and off-label use of biologic and immunomodulatory drugs (Marasca et al., 2018, 2019). This research is essential to expand therapeutic options for patients, many of whom remain undertreated. Herein, we describe repurposing the well-known chemotherapeutic drug, methotrexate, and report a series of patients with HS who responded favorably to long-term methotrexate monotherapy.

Methods

This study was approved by the Institutional Review Board at Beth Israel Deaconess Medical Center (BIDMC). We performed a single-center, retrospective chart review to evaluate patients with HS who were treated with methotrexate at BIDMC between 2000 and 2018. Patients were identified using search terms “hidradenitis suppurativa” or the corresponding International Classification of Diseases 9 or 10 codes 705.83 and L73.2, respectively, in conjunction with “methotrexate.” Comorbidities, concurrent medications, demographics, HS disease severity, laboratory test values, methotrexate dose, and side effects were evaluated. HS disease severity was assessed using the HS Physician Global Assessment (HS PGA; ranging from 1 [clear] to 6 [very severe]), Hurley Staging (I–III), abscess count, fistula count, and inflammatory nodule count.

Two patients in this analysis were initiated on methotrexate by our group at an outside hospital and transitioned to our subspecialty clinic. For both, an HS PGA score and narrative description of disease activity were available, but detailed lesion counts were not. To account for this, both patients were conservatively estimated to have five inflammatory nodules and two abscesses at baseline. This estimation was based on their clinical examination notes prior to care transfer and the severe characterization of their disease at presentation (Table 1).

Patients were further stratified on the basis of whether they received concomitant biologic therapy with methotrexate to control for biologic-induced improvement. Study data were collected and managed using REDCap electronic data capture tools hosted at BIDMC (Harris et al., 2009, 2019). Wilcoxon signed rank tests were used to assess for significance with the p-value set at 0.05 a priori.

Results

A total of 29 patients met our initial search criteria. Fourteen patients were excluded due to never starting methotrexate or lack of follow-up data. Fifteen patients met our inclusion criteria and had multiple follow-up visits at our institution. The mean age was 43.8 years (range, 24–72 years). Patients were predominantly female (n = 10; 66.7%), white (n = 10; 66.7%), and obese (average body mass index [BMI]: 31.4; Table 1). The most frequently reported comorbidity was acne (n = 6), followed by cardiovascular disease (n = 5). The most common failed prior medications were systemic antibiotics (n = 11). Biologics were trialed and failed in 6 patients (methotrexate without biologics: n = 4; methotrexate with biologics: n = 2). The most common concomitant therapy with methotrexate were oral antibiotics (n = 9).

Seven patients received methotrexate without any concomitant biologic medications (Table 1), and eight patients received methotrexate concomitantly with biologics (adalimumab: n = 6; infliximab: n = 1; ustekinumab: n = 1). On average, the group of patients on methotrexate without biologics was older and had a lower BMI than those treated concomitantly with biologics (Table 2).

At baseline, all patients had an average HS PGA score of 4.4 ± 1.12 (mean ± standard deviation on a 1–6 scale; Table 2). The average inflammatory nodule count was 4.67 ± 3.42, and the average number of fistulas was 2.79 ± 3.53 (Table 2). The disease of patients receiving methotrexate without biologics was, on average, less severe than for those receiving methotrexate with biologics (Table 2).

The modal initial dose of methotrexate was 10 mg/week (range, 7.5–20 mg). The average length of treatment (LOT) for all patients was 11.7 months (range, 1–38 months), and the mean cumulative dose of methotrexate was 520.13 mg (range, 30–1665 mg; Table 1). Patients treated with methotrexate without biologics had a longer LOT and cumulative methotrexate dose (LOT: 14.6 months; dose: 579.21 mg) compared with those receiving concomitant biologics (LOT: 9.1 months; dose: 468.44 mg; Table 2).

Overall, HS PGA scores decreased modestly, but not significantly (p = 1.00; Table 2). Patients without biologics showed improvements in HS PGA scores, but those treated with biologics slightly worsened during the treatment course (Table 2). The average number inflammatory nodules decreased in the methotrexate-without-biologics group (baseline: 3.57; final: 1.86; p = .38) and increased in patients treated with methotrexate and biologics (baseline: 5.63; final: 6.50; Table 2). All abscesses in the methotrexate-without-biologics group (n = 4) resolved over the treatment course. There was no significant change in fistula count (p = .69).

Methotrexate was generally well tolerated. Five patients reported self-resolving gastrointestinal disturbances, and one patient had elevated alkaline phosphatase levels that did not interfere with treatment.

Discussion

Methotrexate is an antimetabolite analog of folic acid that inactivates dihydrofolate reductase, an enzyme crucial to thymidine synthesis (Jolivet et al., 1983). Historically, methotrexate has been used to treat cancer and autoimmune diseases, such as psoriasis and rheumatoid arthritis. Our hypothesis regarding methotrexate’s efficacy in HS is partially rooted in its downregulation of neutrophil chemotaxis (Cronstein et al., 1991; O’Callaghan et al., 1988; Waldsorfer et al., 1983).

HS is often characterized by leukocytosis, neutrophilia, pus drainage, and abscess and fistula formation (Miller et al., 2016). Neutrophils are particularly abundant in the deep infiltrate of HS lesions (Lima et al., 2016); therefore, methotrexate’s effects on neutrophils may be particularly beneficial in treating patients with an abscess-predominant HS phenotype (Jekic et al., 2019). However, methotrexate’s effect on neutrophils may not entirely explain its mechanism in HS. Colchicine, another anti-inflammatory medication that also decreases neutrophil chemotaxis, does not appear to offer any benefit in patients with HS (van der Zee and Prens, 2011).

Methotrexate has also been found to suppress NF-κB, a downstream tumor necrosis factor (TNF) alpha-activated inflammatory mediator and a known target of HS therapy (Jekic et al., 2019). Furthermore, methotrexate appears to decrease IL-17 levels in patients with psoriasis through enhancement of regulatory T-cell function (Yan et al., 2018). Increased IL-17 has been identified in HS lesional skin, and reports of anti-IL-17 therapy effectiveness suggests that IL-17 modulation may affect HS disease progression (Marasca et al., 2019; Matusiak et al., 2017; Prussick et al., 2019).

Despite these mechanistic explanations for its potential efficacy, methotrexate is not well described or often prescribed in HS. In an analysis of the National Ambulatory Medical Care Survey from 1990 to 2009 and the MarketScan Medicaid Database from 2003 to 2007, no patients received methotrexate for HS (Davis et al., 2018).
Table 1
Characteristics of patients treated with methotrexate without biologics.

| Patient number | 1      | 14     | 15     | 18     | 19     | 20     | 21     |
|---------------|--------|--------|--------|--------|--------|--------|--------|
| Age           |        |        |        |        |        |        |        |
| Sex           | Female | Female | Female | Male   | Male   | Female | Male   |
| Body mass index | Overweight | Overweight | Obese | Morbidly obese | Obesity | Normal | Normal |
| Comorbidities | Coronary artery disease, hirsutism, hyperlipidemia | Adalimumab (stopped in setting of new onset alopecia areata) | Adalimumab (intraleisional triamcinolone, red light photodynamic therapy, wide local excision to bilateral axillae) | Adalimumab (stopped due to neuropathy, clindamycin topical, doxycycline, intraleisional triamcinolone, tetracycline) | Amoxicillin-clavulanate | Cephalexin | None |
| Prior failed treatments | Not documented | Adalimumab (stopped in setting of new onset alopecia areata) | Adalimumab (intraleisional triamcinolone, red light photodynamic therapy, wide local excision to bilateral axillae) | Adalimumab (stopped due to neuropathy, clindamycin topical, doxycycline, intraleisional triamcinolone, tetracycline) | Amoxicillin-clavulanate | Cephalexin | None |
| Concomitant medications for hidradenitis suppurativa | Minocycline, prednisone, spironolactone | Benzoyl peroxide, clindamycin topical, spironolactone | Clobetasol cream, spironolactone | Minocycline | Benzoyl peroxide, clindamycin topical, spironolactone | Clobetasol cream, spironolactone | Minocycline | None |
| Areas involved | Inguinal folds, perianal, perineum | Axillae, inframammary inguinal folds, buttocks | Axillae, inframammary, left inguinal fold | Buttocks, left inguinal fold, scrotum | Buttocks, inguinal folds, intergluteal cleft, perineum | Axillae, left buttock, mons pubis | Right axilla, buttocks, groin, intergluteal cleft |
| HS PGA baseline | Severe | Moderate | Moderate | Very severe | Mild | Moderate | Very severe |
| HS PGA end of treatment | Minimal | Moderate | Moderate | Minimal | Mild | Mild | Moderate |
| Inflammatory nodules baseline | 5* | 4 | 5 | 5 1 | 2 | 3 | 1 |
| Inflammatory nodules end of treatment | 1 | 4 | 2 | 0 | 2 | 2 | 2 |
| Fistulas baseline | NR | 1 | 0 | NR | 0 | 2 | 6 |
| Fistulas end | NR | 1 | 0 | 0 | 0 | 0 | 6 |
| Abscesses baseline | 2* | 0 | 0 | 2 1 | 0 | 0 | 0 |
| Abscesses end of treatment | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

HS PGA, Hidradenitis Suppurativa Physician's Global Assessment; NR, not recorded.

* Conservative estimate based on the following narrative description: “Disease confined to perineum, perianal, and inguinal area. Numerous large plaques of indurated erythema and scarring.”

1 Conservative estimate based on the following narrative description: “Almost diffuse involvement and multiple interconnected sinus tracts and abscesses across the buttocks, and also involving the groin and scrotum.”
Levels (Martinez-Feito et al., 2019). Methotrexate’s lack of additional clinical response and prolonged anti-TNF therapeutic activity does not appear to offer additional benefit in patients receiving methotrexate as a monotherapy. Additionally, a dose response may be partially responsible for the use of methotrexate in a more diverse patient population because patients in our cohort were predominantly white and female.

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**Study Approval**

The author(s) confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies.

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