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Original Research

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.

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.

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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 (Barrea 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 2). 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; Walsdorfer 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-kB, 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

Table 1
Characteristics of patients treated with methotrexate without biologics.

Patient number	1	14	15	18	19	20	21
Age	72	37	60	68	35	52	52
Sex	Female	Female	Female	Male	Male	Female	Male
Body mass index	Overweight	Obese	Morbidly obese	Overweight	Normal	Normal	Normal
Comorbidities	Coronary artery disease, hirsutism, hyperlipidemia	Alopecia areata, acne vulgaris	Obesity	Coronary artery disease, hyperlipidemia, hypertension	Nodulocystic acne, pilonidal cyst, Raynaud's syndrome	Carpal tunnel syndrome, depression, myofascial pain syndrome, pilonidal cyst	Herniated disk, osteoarthritis, pilonidal cyst
Prior failed treatments	Not documented	Adalimumab (stopped in setting of new onset alopecia areata)	Adalimumab (intralesional triamcinolone, red light photodynamic therapy, wide local excision to bilateral axillae)	Not documented	Adalimumab (stopped due to neuropathy, clindamycin topical, doxycycline, intralesional triamcinolone, tetracycline)	Adalimumab (stopped due to allergic reaction, clindamycin topical, oral contraceptive agents)	Cephalexin
Concomitant medications for hidradenitis suppurativa	Minocycline, prednisone, spironolactone	Benzoyl peroxide, clindamycin topical, spironolactone	Clobetasol cream, spironolactone	Minocycline	Amoxicillin-clavulanate	Cephalexin	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†	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	5
Abscesses baseline	2*	0	0	2†	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."
† 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."

Table 2
Disease characteristics of patients with hidradenitis suppurativa treated with methotrexate.

	Methotrexate with biologics (n = 8)	Methotrexate without biologics (n = 7)	Combined (n = 15)
Age (years)	36.13	52.57	43.80
Average body mass index	33.98	28.44	31.39
Race	4 white, 3 black, 1 Asian	6 white, 1 Hispanic	10 white, 3 black, 1 Hispanic, 1 Asian
Sex	2 male, 6 female	3 male, 4 female	5 male, 10 female
Average length of treatment (months)	9.13	14.57	11.67
Average cumulative dose (mg)	468.44	579.21	520.10
Average inflammatory nodules baseline	5.63	3.57*	4.67*
Average inflammatory nodules end	6.50	1.86	4.33
Average fistulas baseline	3.75	1.5*	2.79*
Average fistulas end	3.00	1.00	2.07
Average abscesses baseline	0.63	0.57†	0.60†
Average abscesses end	1.75	0.00	0.93
Average HS PGA baseline	4.25	3.86	4.40
Average HS PGA end	4.50	3.00	3.80

HS PGA, Hidradenitis Suppurativa Physician's Global Assessment.
* Assumed five inflammatory nodules for two patients (see footnote in Table 1 for more information).
† Assumed two abscesses for two patients (see footnote in Table 1 for more information).

et al., 2015). Improvement in a subset of patients in this analysis differs from the only other report of patients with HS treated with methotrexate, which demonstrated no improvement (Jemec, 2002). Importantly, the patients in that case series received methotrexate as a monotherapy and for a shorter period of time compared with ours, with one patient treated for 6 weeks, one for 4 months, and one for 6 months. A few case reports describe methotrexate use in combination with anti-TNF agents for patients with concurrent HS and synovitis, acne, pustulosis, hyperostosis, osteitis syndrome (Crowley et al., 2018; De Souza et al., 2011; Vekic et al., 2018). Importantly, methotrexate was primarily used for arthritis control, and skin symptoms did not improve until anti-TNF therapy was initiated. Therefore, an additional role may exist for methotrexate in increasing anti-TNF serum levels.

Baseline differences in the demographics of patients receiving methotrexate with and without biologics may inform therapeutic decisions. Methotrexate appeared most effective as a primary therapy in older patients with lower BMIs not receiving biologic therapy. Additionally, a dose response may be partially responsible for improvement because patients with a longer LOT and cumulative dose fared better in terms of disease severity. However, methotrexate does not appear to offer additional benefit in patients receiving biologic therapy. This is in contrast with findings in RA literature, where methotrexate administered concomitantly with anti-TNF enhanced clinical response and prolonged anti-TNF therapeutic levels (Martinez-Feito et al., 2019). Methotrexate's lack of additional benefit in this HS cohort is potentially due to the high baseline disease activity in this group, signaled by the addition of methotrexate to their therapeutic regimen in the first place.

Methotrexate's side effects are well established and include anemia and hepatotoxicity. All patients were screened with a baseline complete blood count, liver function tests, hepatitis panel, and tuberculosis serology prior to initiation. Complete blood counts and liver function tests were repeated 1 month after treatment initiation and every 3 months thereafter.

Conclusion

Methotrexate may represent a viable primary therapy in a certain subset of patients with HS, but it appears ineffective in patients treated in conjunction with biologic therapies. Limitations of this study include its retrospective nature and small sample size. Future directions may include investigations of the use of methotrexate as a strict monotherapy, especially in patients not treated with biologics. Additionally, future studies may investigate 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.

References

Barrea L, Fabbrocini G, Annunziata G, Muscogiuri G, Donnarumma M, Marasca C, et al. Role of nutrition and adherence to the Mediterranean diet in the multidisciplinary approach of hidradenitis suppurativa: Evaluation of nutritional status and its association with severity of disease. Nutrients 2019;11(1):57.
Cronstein BN, Eberle MA, Gruber HE, Levin RI. Methotrexate inhibits neutrophil function by stimulating adenosine release from connective tissue cells. Proc Natl Acad Sci U S A 1991;88(6):2441–5.
Crowley EL, O'Toole A, Gooderham MJ. Hidradenitis suppurativa with SAPHO syndrome maintained effectively with adalimumab, methotrexate, and intralesional corticosteroid injections. SAGE Open Med Case Rep 2018;6. 2050313X18778723.
Davis SA, Lin HC, Balkrishnan R, Feldman SR. Hidradenitis suppurativa management in the United States: an analysis of the National Ambulatory Medical Care Survey and MarketScan Medicaid Databases. Skin Appendage Disord 2015;1(2):65–73.
De Souza A, Solomon GE, Strober BE. SAPHO syndrome associated with hidradenitis suppurativa successfully treated with infliximab and methotrexate. Bull NYU Hosp Jt Dis 2011;69(2):185–7.

Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform 2019;103208.
Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42(2):377–81.
Jekic B, Maksimovic N, Damnjanovic T. Methotrexate pharmacogenetics in the treatment of rheumatoid arthritis. Pharmacogenomics 2019;20(17):1235–45.
Jemec G. Methotrexate is of limited value in the treatment of hidradenitis suppurativa. Clin Exp Dermatol 2002;27(6):528–9.
Jolivet J, Cowan KH, Curt GA, Clendeninn NJ, Chabner BA. The pharmacology and clinical use of methotrexate. N Engl J Med 1983;309(18):1094–104.
Lima AL, Karl I, Giner T, Poppe H, Schmidt M, Presser D, et al. Keratinocytes and neutrophils are important sources of proinflammatory molecules in hidradenitis suppurativa. Br J Dermatol 2016;174(3):514–21.
Marasca C, Annunziata MC, Napolitano M, Fabbrocini G. Unconventional therapies for hidradenitis suppurativa. Expert Rev Clin Pharmacol 2018;11(9):879–87.
Marasca C, Megna M, Balato A, Balato N, Napolitano M, Fabbrocini G. Secukinumab and hidradenitis suppurativa: friends or foes? JAAD Case Rep 2019;5(2):184–7.
Martinez-Feito A, Plasencia-Rodriguez C, Navarro-Compan V, Hernandez-Breijo B, Gonzalez MA, Monjo I, et al. The effect of methotrexate versus other disease-modifying anti-rheumatic drugs on serum drug levels and clinical response in patients with rheumatoid arthritis treated with tumor necrosis factor inhibitors. Clin Rheumatol 2019;38(3):949–54.
Matusiak Ł, Szczęch J, Bieniek A, Nowicka-Suszko D, Szepietowski JC. Increased interleukin (IL)-17 serum levels in patients with hidradenitis suppurativa: Implications for treatment with anti-IL-17 agents. J Am Acad Dermatol 2017;76(4):670–5.
Miller IM, Ring HC, Prens EP, Rytgaard H, Mogensen UB, Ellervik C, et al. Leukocyte profile in peripheral blood and neutrophil-lymphocyte ratio in hidradenitis suppurativa: a comparative cross-sectional study of 462 cases. Dermatol Basel Switz 2016;232(4):511–9.
O'Callaghan JW, Forrest MJ, Brooks PM. Inhibition of neutrophil chemotaxis in methotrexate-treated rheumatoid arthritis patients. Rheumatol Int 1988;8(1):41–5.
Prussick L, Rothstein B, Joshipura D, Saraiya A, Turkowski Y, Abdat R, et al. Open-label, investigator-initiated, single-site exploratory trial evaluating secukinumab, an anti-interleukin-17A monoclonal antibody, for patients with moderate-to-severe hidradenitis suppurativa. Br J Dermatol 2019;181(3):609–11.
Saunte DML, Jemec GBE. Hidradenitis suppurativa: advances in diagnosis and treatment. JAMA 2017;318(20):2019–32.
Slade DEM, Powell BW, Mortimer PS. Hidradenitis suppurativa: pathogenesis and management. Br J Plast Surg 2003;56(5):451–61.
van der Zee HH, Prens EP. The anti-inflammatory drug colchicine lacks efficacy in hidradenitis suppurativa. Dermatology 2011;223:169–73.
Vekic DA, Woods J, Lin P, Cains GD. SAPHO syndrome associated with hidradenitis suppurativa and pyoderma gangrenosum successfully treated with adalimumab and methotrexate: a case report and review of the literature. Int J Dermatol 2018;57(1):10–8.
Walsdorfer U, Christophers E, Schröder JM. Methotrexate inhibits polymorphonuclear leucocyte chemotaxis in psoriasis. Br J Dermatol 1983;108(4):451–6.
Werth JVD, Williams HC. The natural history of hidradenitis suppurativa. J Eur Acad Dermatol Venereol 2000;14(5):389–92.
Yan K, Xu W, Huang Y, Zhang Z, Huang Q, Xin KZ, et al. Methotrexate restores the function of peripheral blood regulatory T cells in psoriasis vulgaris via the CD73/AMPK/mTOR pathway. Br J Dermatol 2018;179(4):896–905.