SKIN

ORIGINAL RESEARCH

Treatment of Pityriasis Rubra Pilaris with Daily Low-Dose Methotrexate: A Retrospective Cohort Study

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ABSTRACT

Background: Pityriasis rubra pilaris (PRP) is a rare disease that can be refractory to many treatments, including corticosteroids, immunomodulatory drugs, and biologics. Available literature has primarily described the use of weekly dosing of methotrexate, but there is limited data investigating the effectiveness of daily low-dose methotrexate in PRP treatment.

Methods: A retrospective cohort study was conducted from September 2010 to December 2019 to determine the effectiveness of daily low-dose methotrexate in treating PRP.

Results: The average duration of follow-up was 13.5 months. 14 patients were treated with oral daily low-dose methotrexate. 13 patients (92.9%) showed improvement on oral daily low-dose methotrexate. Mean time to clinical response was 5.9 weeks. In seven patients (50%), complete response on methotrexate monotherapy occurred within an average of 11.9 months. 12 patients (85.7%) developed asymptomatic elevations in liver enzymes (ALT and AST) that resolved in most patients (66.7%) after dose reduction.

Conclusions: In this study, daily low-dose methotrexate was an effective treatment of PRP and may be considered in patients unresponsive to weekly dosing. Due to the high incidence of elevated liver enzymes, the authors recommend frequent lab monitoring and screening for risk factors. Further studies are warranted to elucidate the efficacy of daily low-dose methotrexate in the management of PRP.

INTRODUCTION

Pityriasis rubra pilaris (PRP) is a rare papulosquamous disorder. Presentation classically features hyperkeratotic follicular papules, scaly salmon-pink plaques, palmoplantar hyperkeratosis, and islands of skin-sparing ("nappes claires").[1,2]

Treatment is notoriously difficult and no high-quality randomized controlled trials exist addressing effectiveness of therapeutic options, which include topical and systemic corticosteroids, phototherapy, retinoids, immunomodulators, and biologics.[3-5] Up to 80% of patients undergo spontaneous resolution within three years of onset, complicating assessment of treatment effectiveness.[1]

Systematic reviews and case series support methotrexate (MTX) as an effective treatment for PRP.[3,6-8] Potential mechanisms of MTX in treating PRP include anti-proliferative and anti-inflammatory effects via reduction of pro-

inflammatory cytokines IL-1, IL-2, IFN-γ, and TNF-α and increasing anti-inflammatory cytokines IL-4 and IL-10.[8,9]

Available literature has primarily investigated weekly dosing of MTX.[2] However, one case series notably observed excellent response rates in patients treated with daily dosing when compared with weekly MTX.[2] While daily dosing is speculated to increase risk of toxicity, one author (KG) has effectively and safely used daily low-dose MTX in treating PRP for over four decades.[2] He has noted success in many cases that were unresponsive to several other treatments, including weekly MTX. Thus, we seek to report our experience with the efficacy of daily low-dose MTX in treatment of PRP.

METHODS

The University of Virginia Institutional Review Board approved this retrospective cohort study. Patients diagnosed with and treated for PRP were identified from the electronic medical record from September 2010 to December 2019. Initial search returned 28 patients diagnosed with PRP based on clinical or histopathologic features. Patients without follow-up after their initial presentation in clinic or those on weekly MTX were excluded. In all, fourteen patients treated with low-dose daily MTX were included in the analysis. Four patients were diagnosed with PRP based on biopsy while the rest were diagnosed clinically. Two of these patients had biopsies at outside hospitals suggestive of parapsoriasis and psoriasis respectively, while five had nonspecific biopsy results.

Patients were most commonly initiated on oral MTX at 2.5 mg six days weekly (Table 1).

Table 1. MTX Dosing regimens (n)

Dosage
2.5 mg for 6 days/wk (9)
2.5 mg for 7 days/week (3)
2.5 mg for 5 days/week (1)
2.5 mg for 6 days/wk + 5 mg on 7th day (1)

Dosing was adjusted based on individual clinical course. Patients that cleared on MTX were tapered off by reducing the weekly cumulative dose by 2.5 mg each month.

Patient demographics and treatment data, including symptoms, prior treatments, MTX dosage, improvement timeline, and adverse effects were collected. Treatment response categories included no response (NR), partial response (PR), and complete response (CR) based on a global assessment. PR was defined as any reduction in involved body surface area whereas CR was defined as the complete clearance of the rash. Therapeutic response time was recorded as the time from MTX initiation to first observed improvement in involved BSA, erythema, or pruritus.

RESULTS

Table 2 depicts the patient cohort demographics. The average age of patients was 63 years (SD = 12.5). Table 3 summarizes each patient in the study. The majority (78.6%) of patients' rashes had failed multiple treatments including topical and systemic corticosteroids, cyclosporine, acitretin, adalimumab, apremilast, ustekinumab, and weekly methotrexate. Treatment failure was defined as either the absence of clinical improvement on a therapy or when an adverse reaction to the medication occurred.

Daily MTX treatment showed a 92.9% response rate with a PR occurring in 42.9% and CR occurring in 50% of patients. Mean

Table 2. Patient demographics

Characteristics (n=14)	
Mean age	63
Males/Females	12/2
Previous treatments, n (%)	
Topical corticosteroids	7 (50%)
Oral steroids	7 (50%)
Cyclosporine	1 (7.1%)
Acitretin	1 (7.1%)
Adalimumab	2 (14.2%)
Apremilast	1 (7.1%)
Ustekinumab	2 (14.2%)
Weekly methotrexate	3 (21.4%)
Previous diagnoses, n (%)	
Psoriasis	3 (21.4%)
Para-psoriasis	1 (7.1%)
Allergic contact dermatitis	2 (14.2%)
Comorbidities predisposing to transaminitis, n (%)	3 (21.4%)
Diabetes mellitus	2 (14.2%)
Hyperlipidemia	2 (14.2%)
Current or previous alcohol use	3 (21.4%)
Baseline elevated transaminases	
Mean duration of follow-up	13.5 months
Rate of loss to follow-up	14.3% (2/14)

time to any clinical response was 5.9 weeks (SD = 3.2) and mean time to CR was 11.9 months (SD = 5.7). As of December 2019, to the authors' knowledge, all patients that achieved CR remain disease-free.

A complete blood count and liver enzymes (ALT and AST) were checked every few months at follow-up visits while patients were on MTX. Elevations in ALT and/or AST were the most common adverse effect, occurring in 12 (85.7%) patients. None of these patients had previously documented hepatic or renal disease. Eleven of these patients had available ALT and AST levels in our medical record system and most (72.7%) were less than three times the upper limit of normal. The mean ALT value in these patients (n=11) was 128.6 units/L (SD = 58.9) while the average AST was 76.9 units/L (SD = 48.1). All patients were asymptomatic and none required hospital admission. Two patients had persistently elevated liver enzymes between four and five times the upper limit of normal that resolved within four weeks of dose reduction. One patient discontinued MTX and switched to acitretin due to persistent mild elevations in ALT and AST and inability to afford frequent lab draws. 35.7% of patients experienced other side effects including mucositis, dizziness, stinging sensation of skin, and decrease in hemoglobin.

Two patients (7 and 13) transitioned either to ixekizumab or acitretin due to lack of efficacy and both achieved CR on the subsequent agent. Patient 4 responded to daily low-dose MTX after failing adalimumab and ustekinumab. Three patients (1, 6, and 13) were previously on weekly MTX (25 mg, 15 mg, and 25 mg respectively) before starting daily dosing. Patient 1 achieved further improvement on daily low-dose MTX while patient 6 achieved CR on daily dosing. Patient 8 achieved CR once ixekizumab was added to MTX.

DISCUSSION

There is a lack of high-quality evidence guiding treatment of PRP. One treatment algorithm recommends topical corticosteroids and systemic retinoids as first-line, MTX as second-line, and biologics as third-line.[5] However, the optimal dosing, duration of therapy, and route of MTX for treating PRP are not established. Knowles and colleagues treated six men with refractory PRP with intermittent intravenous, intermittent intramuscular, intermittent weekly oral, and daily oral MTX.[2] They found that oral MTX, alternating between 5 mg and 2.5 mg daily, required fewer total weeks to achieve remission and demonstrated a lower

Table 3. Summary of Patients

Patient	Age (y)	Gender	MTX dose	Outcome	Reported adverse effects
1	63	F	2.5 mg every day	PR	Mucositis
2	64	M	2.5 mg daily for 6 days/week	CR	Elevation in liver enzymes
3	43	M	2.5 mg daily for 6 days/week	NR; switched to acitretin	Elevation in liver enzymes
4	68	M	2.5 mg daily for 6 days/week	CR	Elevation in liver enzymes
5	72	M	2.5 mg daily for 6 days/week	PR; lost to follow-up	Elevation in liver enzymes, burning sensation of skin
6	81	M	2.5 mg every day	CR	Elevation in liver enzymes
7	67	M	2.5 mg daily for 6 days/week	PR; switched to acitretin	Elevation in liver enzymes
8	68	M	2.5 mg daily for 5 days/week	PR; added on ixekizumab	Elevation in liver enzymes, decrease in hemoglobin
9	71	M	2.5 mg daily for 6 days/week	PR; lost to follow-up	None
10	43	M	2.5 mg daily for 6 days/week	CR	Elevation in liver enzymes
11	67	F	2.5 mg daily for 6 days/week	CR	Elevation in liver enzymes
12	77	M	2.5 mg daily for 6 days/week	CR	Elevation in liver enzymes, decrease in hemoglobin
13	45	M	2.5 mg daily for 6 days/week + 5 mg on 7th day of week	PR; switched to ixekizumab	Elevation in liver enzymes, dizziness
14	50	M	2.5 mg every day	CR	Elevation in liver enzymes

relapse rate compared with intermittent intravenous or intramuscular MTX. Furthermore, two patients who did not respond to either weekly oral, intramuscular, or intravenous MTX subsequently responded to daily oral low-dose MTX.

In this study, daily oral low-dose MTX was effective with 92.9% of patients responding and 50% achieving CR, consistent with the 90.9% overall response rate and 40.9% complete clearance rate reported in a recent review of 44 patients treated with oral or subcutaneous MTX.[8] The mean times to any improvement (5.9 weeks) and to CR (11.9 months) were consistent with reported response times of 3-12 weeks.[8-12] Duration of therapy often lasted several months (range 1-12 months).[8] Because up to 80% of patients with PRP undergo spontaneous remission, it is possible that the natural history of PRP confounds these results.[1]

Elevated liver enzymes were notably very common in this cohort, occurring in 85.7% of patients. All patients were asymptomatic. Most patients' ALT and AST levels were less than three times the upper limit of normal. Elevations in liver enzymes resolved in 66.7% of patients within two to four weeks after dose reduction and only one patient discontinued therapy due to persistently elevated liver enzymes. Predisposing risk factors for MTX-induced hepatotoxicity including alcohol use, diabetes mellitus, hyperlipidemia, and baseline elevated liver

enzymes were seen in 50% of patients.[13] Because daily folic acid supplementation may decrease the efficacy of MTX, 78.6% of patients were not on folic acid, which can increase risk of hepatotoxicity.[13,14] The rates of elevated liver enzymes with MTX in this study were higher than that reported in the literature. One randomized controlled trial in patients with generalized plaque psoriasis found that 44% of patients experienced liver enzyme elevation on daily MTX.[15] In contrast, 33% of patients on weekly MTX experienced liver enzyme elevation.[15] However, daily administration resulted in less nausea, vomiting, and fatigue.[15] The rates of elevated liver enzymes in patients with PRP on MTX may be underreported in the literature, which consists mainly of studies with small sample sizes. Furthermore, patients with PRP tend to be elderly and may have comorbidities increasing their susceptibility to side effects. The decision to start MTX therapy on patients with PRP should be based on the patient's medical history. For those with few comorbidities predisposing to hepatotoxicity on MTX, the benefits of MTX therapy may outweigh the risks. Providers should monitor strictly with routine labs and screen for risk factors before starting MTX.

Clinicians should consider cost when selecting treatment agents given the typical duration of therapy until remission in PRP (11.9 months). Cost-effectiveness analyses estimate the annual costs of adalimumab in treating psoriasis to be $23,538, while newer interleukin-17 inhibitors cost between $37,224 (brodalumab) and $64,396 (ixekizumab).[16,17] In contrast, MTX 7.5 mg weekly costs only $1,197.[16]

Limitations of this study include small sample size and its retrospective nature. The mean duration of follow-up in this study was only 13.5 months (Table 2) and two patients (14.3%) were lost to follow-up. Magnitude of BSA improvement and time to achieve CR in this cohort were difficult to objectively measure. Inconsistent follow-up intervals may also introduce bias.

CONCLUSION

Treatment of PRP is challenging. Various routes and dosages of MTX can induce remission. In this study, oral daily low-dose MTX was an effective treatment of PRP. The markedly lower financial cost and availability of MTX make it a favorable option. Furthermore, a trial of daily low-dose MTX may be considered for patients unresponsive to weekly dosing. Due to the high incidence of elevated liver enzymes in this cohort, the authors recommend frequent lab monitoring and appropriate screening for hepatotoxicity risk factors. Further randomized controlled trials are warranted to elucidate the efficacy of oral daily low-dose MTX in PRP management.

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