Value of adding betamethasone pulse therapy to methotrexate in treating patients with psoriasis

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Background: Psoriasis is an immune-mediated inflammatory disease with unclear pathophysiology. Although diverse medications have been applied, a paucity of knowledge is accessible regarding the use of corticosteroids for psoriasis management. We evaluated the efficacy of corticosteroid pulse therapy in combination with methotrexate versus methotrexate alone for psoriasis treatment.

Methods: This cohort study was conducted on 51 hospitalized patients with erythrodermic or pustular psoriasis who were assigned to one of the therapeutic interventions of subcutaneous methotrexate alone (n = 33) or in combination with betamethasone pulse therapy (n = 18). The first group was treated with weekly 15 mg subcutaneous methotrexate for six weeks, and the second group received a similar dose of methotrexate plus 3 mg oral betamethasone weekly. The patients were followed for six months and assessed regarding the disease remission, relapses, the interval between the medication and relapse incidence, and patient satisfaction with the regimens.

Results: The studied groups were similar regarding gender ($P = 0.296$), age($P = 0.561$), and the type of cutaneous lesions ($P = 0.807$). Six months follow-up of the two therapeutic interventions revealed insignificant differences in terms of early response to the treatment ($P = 0.993$), the incidence ($P = 0.142$) and frequency of relapses ($P = 0.928$), and the interval period between the treatment and relapse ($P = 0.213$). Besides, the patients' treatment satisfaction did not differ between the groups ($P = 0.453$).

Conclusion: Based on this study, combining methotrexate and low-dose corticosteroid pulse therapy does not lead to better outcomes than methotrexate alone for managing pustular and erythrodermic psoriasis. Further studies are strongly recommended.

Keywords: psoriasis, methotrexate, betamethasone, recurrence

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INTRODUCTION

Psoriasis is an immune-mediated inflammatory disease with unclear pathophysiology. It is estimated that 0.1-11.4% of the global population has psoriasis [1]. Psoriasis negatively affects a patient's daily performance, quality of life, and functioning.

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Moreover, the association of this condition with arthritis, cardiovascular diseases, and depression has been documented [2]. Up to 80% of psoriatic patients present mild to moderate symptoms, mostly managed by topical treatments. Nevertheless, systemic oral agents or phototherapy are administered considering the patients' response to the topical treatments, disease severity, and patient characteristics [3].

Since introducing methotrexate for psoriasis treatment, this agent has been applied in different doses and routes [4-7]. Methotrexate is mostly used orally and inhibits dihydrofolate reductase, preventing epidermal proliferation. Besides, this drug has immunosuppressive effects that can limit activated lymphocytes' actions and restrict cytokine production [8]. To achieve a longer period of disease remission and better response to treatment, methotrexate is prescribed in combination with psoralen, ultraviolet A light (PUVA), acitretin, cyclosporine, and infliximab [9-12].

Combining methotrexate with other drugs, such as cyclosporine, retinoids, and biological agents, is costly; therefore, these patients are mostly treated with this agent alone.

Corticosteroids are the other group of medications used for psoriasis. Despite the promising outcomes, the adverse effects of long-term corticosteroid use and the probability of psoriasis relapse have limited their use [13]. Corticosteroids stop cellular growth in the G1 and S phases. Thus, they reduce the mitotic index and suppress lesion progression. The other characteristics of corticosteroids include anti-inflammatory, antiproliferative, and immunosuppressive effects [14].

Considering the paucity of knowledge regarding the concurrent use of methotrexate and corticosteroids for the management and treatment of psoriasis, this study assessed the therapeutic effects of methotrexate alone and in combination with corticosteroid pulse therapy for psoriasis treatment.

METHODS

Study population

The current cross-sectional study was conducted on 51 hospitalized patients with psoriasis admitted at Alzahra Hospital of Isfahan University of Medical Sciences from May 2016 to January 2019.

The study was conducted on all patients above 18 years old who presented their willingness to participate. The exclusion criteria were the reluctance to participate in the study, over 20% defect in the medical records, and failure to connect with the patients for follow-up.

Patients hospitalized and treated with one of the regimens, methotrexate alone or in combination with betamethasone pulse therapy, entered the study by census sampling.

The study was designed single-blinded, as the person who followed the patients and interviewed them was unaware of the therapeutic approach.

Interventions

The interventions were as follows;

The first group (n = 33) was treated with weekly 15 mg subcutaneous methotrexate (each ampule contains 2.5 mg/1 ml drug, Osvah, Iran) for six weeks. The second group (n = 18) was treated with methotrexate in a similar dosage plus a weekly single dose of 3 mg oral pulse betamethasone therapy (Raha, Iran) for six weeks.

Outcomes

Patients' information, including age, gender, and type of psoriasis (pustular or erythrodermic), was recorded in the study checklist.

The patients were revisited by an expert dermatologist at the end of the interventions, and their disease remission was evaluated by assessing the lesions. Other investigations included the period of hospitalization, disease relapse incidence, and frequency of psoriasis relapses within six months after the interventions, the interval between treatment and disease relapse, and the patient's satisfaction with the therapeutic approach.

The patients' satisfaction was assessed using a five-point Likert scale ranging from zero to four as very dissatisfied, dissatisfied, neither satisfied nor dissatisfied, satisfied, and very satisfied.

Data analysis

The obtained data were entered into the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 23. Qualitative data are presented as absolute numbers and percentages, and quantitative as mean and standard deviation. The normality of data distribution was assessed using the Smirnov-Kolmogrov test. Categorical data were compared using the chi-squared test or Fisher's exact test.

Continuous data were compared using the independent t-test (or Mann-Whitney U test if the data were not normally distributed). P-values of less than 0.05 were regarded as significant.

Ethical consideration

The study proposal that met the principles of the Helsinki Declaration was proposed to the Ethics Committee of Isfahan University of Medical Sciences and approved under the code number IR.MUI.MED.REC.1400.589. Then, the study protocol was explained to the patients, and they were reassured about the confidentiality of their personal information and provided written consent.

RESULTS

In the current study, the data of 51 patients in two groups of treatment with methotrexate alone (n = 33) and the combination of methotrexate and betamethasone pulse therapy (n = 18) were evaluated and then followed for six months. The studied population predominantly consisted of males (56.86%) with a mean age of 43.43 ± 17.28 (18–80 years old). The studied patients mostly suffered from the erythrodermic form of psoriasis (58.82%).

Table 1 compares the demographic and clinical characteristics of the studied groups. According to this table, the two groups did not differ in terms of gender ($P = 0.296$), age ($P = 0.561$), and the type of cutaneous lesions ($P = 0.807$).

The assessments revealed that the two therapeutic approaches were not statistically different in terms of early response to treatment ($P = 0.993$), incidence ($P = 0.142$) and frequency of relapses ($P = 0.928$), and the interval period between the treatment and relapse ($P = 0.213$). Besides, the patients' treatment satisfaction was similar between the groups ($P = 0.453$) (Table 2).

Table 3 compares the outcomes of the therapeutic interventions across the two genders. Based on this table, the interventions did not differ regarding the rate of remission, relapse, the interval between treatment and relapse occurrence, the frequency of relapses, and patient satisfaction with the therapeutic approach ($P > 0.05$).

Table 1. Demographic and clinical characteristics of the studied population

	Methotrexate alone (n = 33)	Methotrexate plus betamethasone pulse therapy (n = 18)	*P*-value
Age (years), mean ± standard deviation	44.73 ± 18.17	41.06 ± 17.48	0.561*
Gender n (%)			
Male	17 (51.5)	12 (66.7)	0.296**
Female	16 (48.5)	6 (33.3)	
Psoriatic lesions, n (%)			
Pustular	14 (42.5)	7 (38.9)	0.807**
Erythrodermic	19 (57.6)	11 (61.1)	
Hospitalization period (days), mean ± standard deviation	11.00 ± 3.85 (range: 3-20)	16.94 ± 9.65 (range:7-45)	0.009*

* Mann-Whitney U test
** Chi-squared test

Table 2. Treatment outcomes with each regimen

	Methotrexate alone (n = 33)	Methotrexate plus betamethasone pulse therapy (n = 18)	*P*-value
Remission, n (%)	26 (78.8)	14 (77.8)	0.933*
Relapse, n (%)	19 (57.6)	14 (77.8)	0.149*
Frequency of relapses within 6 months after hospitalization, mean ± standard deviation	2.21 ± 1.47	2.50 ± 2.17	0.928**
The interval between treatment and disease relapse (months), mean ± standard deviation	4.98 ± 4.78	3.00 ± 2.79	0.213**
Satisfaction with the therapeutic regimen, mean ± standard deviation	3.45 ± 0.83	3.17 ± 1.09	0.453**

* Chi-squared test
** Mann-Whitney Utest

Table 3. Comparison of treatment outcomes with each regimen in patients.

	Methotrexate alone (n = 16)	Methotrexate plus betamethasone pulse therapy (n = 6)	*P*-value	Methotrexate alone (n = 33)	Methotrexate plus betamethasone pulse therapy (n = 18)	*P*-value
Lesion type						
Pustular	9 (56.3)	2 (33.3)	0.635*	5 (29.4)	5 (41.7)	0.694*
Erythrodermic	7 (43.8)	4 (66.7)		12 (70.6)	7 (58.3)	
Remission, n (%)	12 (74)	6 (100)	0.541*	14 (82.4)	8 (66.7)	0.403*
Relapse, n (%)	9 (56.3)	5 (83.3)	0.351*	10 (58.8)	9 (75)	0.409*
Frequency of relapses within 6 months after hospitalization, mean ± standard deviation	2.22 ± 1.30	3.00 ± 2.34	0.666**	2.20 ± 1.68	2.22 ± 2.16	0.720**
The interval between treatment and disease relapse (months), mean ± standard deviation	6.39 ± 5.14	1.25 ± 0.50	0.192**	4.38 ± 3.04	4.00 ± 3.10	0.699**
Patients' satisfaction with the therapeutic regimen, mean ± standard deviation	3.44 ± 0.89	3.33 ± 1.03	0.99**	3.47 ± 0.80	3.08 ± 1.16	0.394**

* Fisher's exact test
** Mann-Whitney U test

DISCUSSION

The anti-inflammatory and antiproliferative characteristics of corticosteroids have made these agents intriguing compounds for immune-mediated disorders. The relapsing course of psoriasis and the adverse effects of long-term corticosteroid use have limited the chronic administration of these agents for psoriasis treatment. This is while methotrexate has been widely accepted as an appropriate treatment option since long ago. Nevertheless, the recurrent relapses of the lesions in some types of the disease, such as erythrodermic and pustular forms of psoriasis, have lent attention to combination therapies [15]. Therefore, we investigated the efficacy of methotrexate therapy versus its combination with corticosteroid pulse therapy for managing psoriatic lesions in hospitalized patients.

The findings of this study revealed that the treatment with methotrexate alone or in combination with corticosteroids differed neither in response to treatment nor in the prevention of relapses. Gender-based assessments of the regimen's influence on the disease also showed insignificant differences. However, it should be noted that the treatment period was longer among those who applied corticosteroid pulse therapy, which may represent a more severe course of disease among this group and reflect a source of bias in patient selection. Hence, randomized clinical trials are strongly recommended to generalize the outcomes.

Methotrexate is often used for psoriasis control. Coates *et al.* favored this agent for managing cutaneous and musculoskeletal forms of psoriasis due to its efficacy, drug tolerability, and minimal adverse effects [15]. Besides, concerns regarding the potential complications with methotrexate are negligible, as limited numbers of hepatic failure, cirrhosis, and liver fibrosis have been recorded [16]. The other characteristic favoring methotrexate's use is its flexibility in administration, as the therapeutic dosage and route of application (oral versus intravenous) can be easily altered [4].

Surfing the literature revealed limited information about the effects of corticosteroid pulse therapy plus methotrexate for the systematic treatment of psoriasis. The only study in this regard was conducted by Gupta and colleagues, which, in contrast to the current report, presented that the weekly administration of 15 mg methotrexate plus weekly 3 mg oral betamethasone was accompanied by significant elongation of disease remission and the shortening of the period required for the lesion healing compared with methotrexate alone [14].

Clinicians are often reluctant to use systemic corticosteroids for psoriasis management due to claims that systemic steroids can lead to psoriasis deterioration, disease relapse in more severe courses, and being affected by the pustular form of the disease after regimen cessation [17]. Nevertheless, we found no difference between the two groups regarding the

relapsing rate, the interval between the relapses, and the severity of the relapsed courses; however, this may be due to the short follow-up period of the study.

The other complication that has not only unfavored the use of systemic but also topical steroid agents for psoriasis is the potential increased risk for infection with diverse pathogens, including *Trichophyton rubrum* [18], cytomegalovirus [19], streptococcal species [20], varicella zoster [21] and the Epstein-Barr virus [22] in adults. Streptococcal pharyngitis has also been documented in children following corticosteroid use [23]. It should be noted that chronic steroid use can lead to increased weight, hypocalcemia, mild headache, insomnia, agitation, and acne, though such effects were noted at betamethasone doses of 5-10 mg twice a week for 2-4 months, significantly higher than our study [24]. Despite the mentioned complications of systemic corticosteroids, topical corticosteroids remain second-line treatments for psoriasis [25].

Limitations

The cohort design of this study is one of the most significant limitations. Therefore, further studies with randomized clinical trial designs are strongly recommended to determine an appropriate corticosteroid dose for controlling and treating psoriasis. Besides larger sample populations, the comparison of different steroids and diverse methotrexate doses can help achieve better regimens for the treatment of patients who have uncontrolled psoriasis.

CONCLUSION

Based on this study, the combination therapy of methotrexate and low-dose corticosteroid pulse therapy did not lead to better outcomes than methotrexate alone for managing pustular and erythrodermic psoriasis. Further studies are strongly recommended.

Author's contributions

A.A contributed in the conception of the work, conducting the study, drafting and revising the draft and approval of the final version of the manuscript. F.I contributed in revising the draft and approval of the final version of the manuscript. Z.SH contributed in the drafting and revising the draft. S.Kh and M.S analyzed data. All the authors approved the final version.

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