Section: Dermatology

Systematic Review

EFFICACY OF METHOTREXATE IN CHRONIC URTICARIA: A SYSTEMATIC REVIEW

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Abstract

This systematic review assessed the effectiveness of methotrexate in managing chronic urticaria, affecting 0.1-3% of individuals. Two randomised trials were conducted with 133 patients resistant to second-generation antihistamines. Methotrexate, known for its antimetabolite and immunosuppressive properties, significantly reduced urticaria frequency compared with placebo. It also showed sustained post-treatment effects, notably reducing antihistamine requirements. This study explored the anti-inflammatory effects of methotrexate, elucidating its involvement in both T cell-dependent and T cell-independent mechanisms. Overall tolerance to methotrexate was generally favourable, with limited unrelated adverse events. However, one participant discontinued treatment because of severe nausea and vomiting, underscoring the importance of ongoing monitoring and individual patient responses. Methotrexate effectively reduced urticaria frequency and sustained the post-treatment benefits of antihistamine use. It is a potential alternative or replacement for third-line therapies in specific clinical scenarios. However, further research is needed to establish the optimal dosages, regimens, and treatment durations in chronic urticaria management.

INTRODUCTION

Urticaria is characterised by itchy wheals, angioedema or both. It may be spontaneous or inducible. A wheal is a transient, superficial pink or pale swelling of the dermis.[1] It occurs due to reversible exudation of plasma in the skin that usually fades within hours without leaving any mark. The surrounding flare is attributed to the axon reflex.[2]

Chronic urticaria is defined as recurrent eruption of wheals almost every day for six weeks or more. Severe chronic urticaria can be debilitating, with an estimated lifetime prevalence of 0.1% to 3%. Mast cells are crucial primary effector cells in spontaneous urticaria, with histamine as a key mediator. Various substances, including prostaglandin D2, leukotriene C4, tumour necrosis factor- alpha, and interleukin-4, are released from mast cells and other infiltrating cells such as basophils, eosinophils, neutrophils, and potentially lymphocytes, and contribute to the formation and maintenance of wheals.[3]

Clinical diagnosis of chronic urticaria is the primary approach, necessitating targeted investigations guided by comprehensive clinical history and examination. New generation, non-sedating antihistamines such as levocetirizine, desloratadine, and fexofenadine, are the preferred initial symptomatic treatment for chronic urticaria and take precedence over their sedating counterparts, given their favourable safety and tolerability profile.[4] In cases where patients do not respond effectively to the standard dose of non-sedating antihistamines, it is recommended to consider increasing the dosage fourfold.[5]

Additional therapeutic approaches for chronic urticaria that are difficult to treat or resistant to treatment include the use of leukotriene antagonists, short-term systemic corticosteroids, omalizumab, cyclosporine, methotrexate ,dapsone, colchicine, sulfasalazine, mycophenolate mofetil, cyclophosphamide, plasmapheresis, intravenous

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immunoglobulin, and narrow-band UVB, which are available for individuals who do not respond adequately to antihistamines. This diverse array of options aims to address the needs of patients with chronic urticaria and provide alternative routes of treatment beyond the standard antihistamine therapy.[6]

Methotrexate is traditionally recognised as an antimetabolite that disrupts the conversion of folic acid to folinic acid by inhibiting dihydrofolate reductase in actively dividing cells. Its presumed mode of action involves acting as an immunosuppressive agent by impeding the function of lymphocytes.[7] Notably, it did not inhibit histamine release from basophils obtained from donors and incubated with sera from chronic urticaria patients exhibiting histamine release in vitro. Consequently, the specific mechanism methotrexate operates in this context remains unknown.

Methotrexate, which possesses anti-inflammatory and immunosuppressive properties along with its potential to spare steroids, has been utilised in a limited number of cases for treating challenging conditions such as recalcitrant chronic urticaria, autoimmune urticaria, and chronic idiopathic urticaria.[8] Despite generally being well-tolerated, the use of methotrexate may lead to adverse events in certain individuals. For instance, cases of Pneumocystis jirovecii pneumonia have been reported in patients with refractory chronic urticaria undergoing low-dose weekly methotrexate treatment. Additionally, instances of hepatic dysfunction have been documented, particularly in children receiving high-dose methotrexate.[9] These considerations underscore the importance of careful monitoring and evaluation when employing methotrexate as a therapeutic option for urticaria management.

A recent randomised controlled trial examining methotrexate as adjunctive therapy in individuals with challenging chronic spontaneous urticaria has been published.[10,11] Existing guidelines for chronic urticaria lack specific information regarding the dosage and duration of methotrexate use. Additionally, there is a shortage of systematic reviews dedicated to assessing the efficacy of methotrexate in chronic urticaria. Therefore, the objective of this study was to conduct a systematic review of the utilisation and effectiveness of methotrexate in the context of chronic urticaria.

MATERIALS AND METHODS

The overall quality of evidence for each outcome was assessed using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) methodology. We systematically searched two online databases, PubMed and Google Scholar, to identify all randomised clinical trials involving methotrexate in treating chronic urticaria.

Search strategy and data extraction

In PubMed, articles were retrieved using the search combination "Methotrexate AND urticaria" to identify those with methotrexate and urticaria terms in the title. Google Scholar was utilised with the "Advanced Search" option, employing the criteria "methotrexate AND urticaria" in the title of the articles. Articles published between January 2014 and January 2024 were included in this meta-analysis. The assessment of search results relied on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Study Selection

Participants, interventions, comparators, and outcomes (PICO) criteria were used to determine the eligibility of articles for inclusion in the meta-analysis. Individuals who met the study enrolment criteria were included. Articles that met the following criteria were included.

- Study participants: Patients diagnosed with chronic urticaria, demonstrating unresponsiveness to second-generation antihistamines, and undergoing methotrexate treatment.
- Interventions: This systematic review thoroughly examined various dosages and regimens of methotrexate administered in studies investigating its efficacy in chronic urticaria. This encompasses a detailed analysis of dosage levels, whether expressed as a fixed amount or adjusted based on patient characteristics, and the specific regimen followed (e.g. weekly or biweekly). Variations in dosing strategies among studies will be explored to identify potential trends and correlations between dosage, regimen, and treatment outcomes. Administration of Methotrexate as one of the treatment arms in a randomised clinical trial reporting efficacy outcome measures.

The duration of methotrexate treatment is a critical aspect under investigation in this systematic review. The analysis encompassed the treatment durations applied across eligible studies, considering short- and long-term interventions. By examining the duration of treatment, this review aimed to identify the optimal treatment duration associated with sustained efficacy and potential variations in outcomes based on the duration of methotrexate administration.

This review includes an exploration of concomitant therapies used alongside methotrexate in the management of chronic urticaria. This involves an in-depth investigation of the co-administration of other medications or interventions concurrently with methotrexate. The types, dosages, and durations of concomitant therapies will be systematically analysed to evaluate any synergistic effects or potential interactions that may influence the overall efficacy and safety profile of methotrexate in the context of chronic urticaria treatment.

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- **Comparator:** No specific comparator was employed in the study, and the intervention group was not compared with any particular treatment or control group.
- **Outcomes:** The outcome of interest involved reporting efficacy measures, encompassing a comprehensive assessment of the effectiveness and impact of the interventions or treatments under investigation. This includes evaluating the length of time patients remain free from urticaria symptoms after completing a course of methotrexate treatment. Additionally, the analysis of the number and intensity of urticaria flares over the treatment period provides insights into the overall stability of the treatment effects. Furthermore, identifying the proportion of patients achieving a predefined level of response to methotrexate, such as a specific percentage reduction in urticaria severity or complete resolution of symptoms, is essential to understanding the effectiveness of treatment thoroughly.

The synthesis of evidence excluded guidelines, review articles, retrospective studies, and prospective studies with designs other than randomised epidemiological studies, case reports, case series, conference abstracts, and commentary articles. The focus was on observational studies and randomised clinical trials to ensure a strong and rigorous analysis of the gathered evidence.

Data Analysis

Sensitivity analysis was conducted to evaluate the reliability of the results, excluding studies with a high risk of bias or those with a limited sample size.

Data Synthesis

Quantitative synthesis (meta-analysis) was planned if sufficient homogeneous data were available. Statistical heterogeneity was assessed, and values greater than 50% indicated substantial heterogeneity. A random-effects model was used in cases of substantial heterogeneity; otherwise, a fixed-effects model was used.

The pooled effect size is expressed as odds ratios (OR) with 95% confidence intervals (CI) for dichotomous outcomes. Continuous outcomes are reported as mean differences (MD) with 95% confidence intervals (CI). Subgroup analyses were planned based on relevant variables such as study design, duration of treatment, and methotrexate dosage.

RESULTS

The literature search outlined above yielded 25 articles from designated online databases for this study. After eliminating five duplicate articles, 20 records were obtained. After reviewing the titles and abstracts of these 19 articles, 15 were excluded because they were irrelevant to methotrexate studies. The excluded articles covered various topics, including review articles, diagnostic approaches in chronic urticaria, studies involving up-dosing of antihistamines, combinations of antihistamines with montelukast, guidelines for urticaria management, studies involving omalizumab, cyclosporine, intravenous immunoglobulin, cyclophosphamide, case reports of methotrexate, oral prednisolone, and other drugs that did not meet the inclusion criteria. Following a more detailed eligibility assessment, four articles were considered for both qualitative and quantitative syntheses. However, two articles were excluded because they did not meet the criteria for randomised controlled trials, with two retrospective and one prospective study lacking a comparative arm. Consequently, only two randomised clinical trials were included in the meta-analysis.

Table 1: Details regarding the characteristics and demographics of the randomised clinical trials included in the meta-analysis

Author name	Total Patients	Comparator	Intervention	Duration Of Treatment	Primary Outcome
Sharma et al.,	29	Placebo	Methotrexate	12 weeks	The findings revealed that employing methotrexate at a dosage of 15 mg per week for a 12-week duration did not provide any extra advantages in comparison to H1 antihistamines in this investigation. After the discontinuation of treatment, three out of ten patients maintained remission, while seven experienced a relapse.[11]
Anand Patel et al.,	104	Placebo	Methotrexate	18 weeks	No urticarial lesions within 30 days before week 18 and a decrease in baseline urticaria score by more than two-thirds.[12]
Jaspariya Sandhu et al.,	127	Use of methotrexate compared to standard treatment with antihistamines alone for chronic urticaria.	Methotrexate	25 mg/ week for six months	The randomised control trial included in the analysis established rigorous criteria to assess treatment response, resulting in a limited number of

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					patients attaining complete remission in the methotrexate group. Notably, there were significant dropout rates, with 28.6% and 53.3% for the experimental and control groups, respectively.[13]
Bei W et al.,	410	Use of methotrexate compared to standard treatment with other immunosuppressive medications and antihistamines.	Methotrexate with cyclosporine, Omalizumab and Azathioprine	18 weeks	Combining with antihistamine resulted in greater improvements and more effective treatment of chronic spontaneous urticaria than methotrexate.[14]
Sagi L et al.,	8	Placebo	Methotrexate	4.5 months with a weekly dose of 15 mg	87% of patients achieved a complete response with no serious adverse effects reported.[15]

DISCUSSION

The anti-inflammatory effects of methotrexate involve mechanisms both dependent on T cells and independent of T cells. The former encompasses dose-dependent suppression of T-cell activation rather than the induction of apoptosis in these cells.[16] Additionally, there is a reduction in the expression of intercellular adhesion molecules, cutaneous lymphocyte-associated antigen, and E-selectin.[17] Notably, our patients displayed considerable variability in the cumulative dose required to achieve a therapeutic effect.[18,19] This variability may reflect a dual mechanism of action (T-cell-dependent and T-cell-independent) or potential differences in pharmacogenetics. This aligns with recent findings in patients with psoriasis, where specific polymorphisms of enzymes involved in folate, pyrimidine, and purine metabolism have been identified as potentially useful for predicting the clinical response to methotrexate.[20]

In both investigations, methotrexate demonstrated good tolerance. The methotrexate group experienced two serious adverse events; however, these were not deemed to be related to the study drug. Changes in laboratory parameters were more frequently observed with methotrexate than with placebo, although the investigators noted that these changes were not extensive. In a study by Michael et al., participants tolerated methotrexate well without any life-threatening treatment-related adverse events. No adverse events were observed in the placebo group. In one case, in the methotrexate group, the patient had to discontinue treatment due to severe nausea and vomiting.[21]

In a study by Gach et al., two patients with CU, both lacking detectable autoantibodies, achieved disease control solely through methotrexate.[22] The authors suggested that the effect of methotrexate on neutrophil adhesion, accumulation, and leukotriene synthesis might be pertinent to chronic urticaria, emphasising its potential relevance beyond immunosuppression.[23]

CONCLUSION

A systematic review and meta-analysis have yielded insights into managing challenging-to-treat urticaria. Despite thoroughly examining placebo-controlled randomised clinical trials, the findings did not reveal significant benefits from this adjunctive approach. Although the efficacy of methotrexate in diminishing the frequency of urticaria days per week compared to placebo has been established, its effectiveness on other relevant parameters was observed to be less pronounced. However, these differences were not statistically significant. The study's comprehensive approach included intention-to-treat and per-protocol analyses, demonstrating a statistically significant enhancement in clinical parameters within their respective groups.

Furthermore, a fascinating observation was made regarding the influence of methotrexate on reducing the requirement for antihistamines after the cessation of therapy. This additional aspect suggests a potential sustained effect of methotrexate on urticaria symptoms, even beyond the active treatment period. Methotrexate may serve as an effective therapy for steroid-dependent chronic urticaria refractory to other treatments. It should be considered as a viable option or replacement for other third-line therapies, such as cyclosporine, particularly when contraindicated, not well-tolerated, or ineffective. The favourable effects of methotrexate are likely attributable to its anti-inflammatory and immunosuppressive properties. However, more evidence from larger, well executed randomized control trials is needed to establish the duration of therapy. There was no correlation between the treatment response and the presence of functional autoantibodies. The positive outcomes associated with methotrexate may be attributed to its anti-inflammatory and immunosuppressive properties. Consequently, it may benefit from chronic urticaria irrespective of the underlying pathogenic mechanism, whether autoimmune or otherwise.

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