The therapeutic role of methotrexate in chronic urticaria: A systematic review

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Abstract

Background: Chronic urticaria, in many cases, has an unsatisfactory response to antihistamines. The current recommendations in urticaria do not mention the dose and duration for methotrexate.

Aims: This study aims to systematically review the use/efficacy of methotrexate in chronic urticaria.

Methods: A systematic search in four databases, that is, PubMed/Medline, Cochrane central, Google Scholar and Clinicaltrials.gov was done to identify studies on the use of methotrexate in chronic urticaria using key words "methotrexate [MeSH terms]" and "urticaria" or "urticaria, chronic" or "urticaria, chronic spontaneous."

Results: Nine articles (study participants 127), including three randomized control trials, one prospective interventional trial without control, three retrospective reviews and two case reports, were identified and finally included in the systematic review. There was a paucity of literature and the three randomized control trials did not show any benefit of methotrexate over antihistamines alone. However, in studies where steroid-dependent cases were given methotrexate, marked benefit was reported with steroid-sparing effect, particularly on methotrexate dose escalation.

Limitations: Due to a paucity of published literature on methotrexate in urticaria, a meta-analysis could not be done.

Conclusion: In chronic recalcitrant or steroid-dependent cases, methotrexate may be a therapeutic agent of interest; however, current evidence does not point to any added advantage in efficacy over antihistamines. More evidence based on larger, well-executed randomized control trials is needed in the future to get more definitive answers.

Key words: Chronic urticaria, methotrexate, non-biological therapy in urticaria, systematic review, urticaria

Plain Language Summary

Chronic urticaria is the appearance of weal or "hives" on the skin that occur on most days for a period longer than 6 weeks. The disease affects less than 1% of the population; however, it can affect the daily life of patients to a great extent. The researchers of this paper are based in India and the work was carried out in the Dayanand Medical College & hospital, Ludhiana, Punjab. The aim of the study was to scientifically review the existing published literature to examine the use of methotrexate (a drug which affects the replication of immune cells in the body by affecting the DNA synthesis during cell division) in chronic urticaria. The authors independently reviewed scientific databases available to look for published articles. Four databases, i.e., PubMed/Medline, Cochrane Central, Google Scholar and *Clinicaltrials.gov* was done to identify studies on the use of methotrexate in chronic urticaria using certain key words {"methotrexate [MeSH terms]" AND "urticaria" OR "urticaria, chronic" OR "urticaria, chronic spontaneous"}. Only nine relevant studies were included and analyzed; there was a paucity of available literature. The evidence for use of methotrexate was not found in the randomized controlled trials; only few studies showed some benefit in patients who were on oral steroids. To conclude, in chronic recalcitrant or steroid-dependent cases, methotrexate may be a useful therapeutic modality; however, more studies to investigate its role in urticaria are needed to strengthen evidence for its use.

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Introduction

Urticaria, defined as a recurrent, evanescent eruption of wheals, can be a rather frustrating condition to treat for a dermatologist. The word urticaria has its roots in the Latin word *urtica;* which means "to burn." Patients, referred by general practitioners, often recant a long list of previously prescribed anti-histamines, when they first reach the dermatologist's office. *It always comes back*: is a common grievance and they seek a more "permanent cure." When urticaria occurs almost every day for six weeks or more, it is then called chronic urticaria. Chronic urticaria can further be classified as spontaneous (specific trigger/cause cannot be identified) and inducible (urticaria can be elicited following a specific trigger).[1]

In the United States, the prevalence of chronic urticaria has been estimated to be 0.23% and is twice as common in women.[2] In a vast majority of cases, a specific cause may not always be found.[3] Treatment can sometimes be unsatisfactory with either a partial or poor response to antihistamines. As per EAACI/GA2LEN/EDF/WAO (EAACI, European academy of allergology and clinical immunology; GA2LEN, global asthma and allergy European network; EDF, European dermatology forum and WAO, World Allergy Organization) guidelines, omalizumab (anti-IgE) has been shown to be very effective and safe in the treatment of CSU. It has also been reported to be effective in chronic inducible urticaria including cholinergic urticaria, cold urticaria and solar urticaria among others.[1] However, the cost is often prohibitive, particularly for patients in developing countries (monthlycost$541–$2706).[4] Furthermore, certain subset of patients may not be suitable candidates for biological therapy or may develop adverse effects to the same.[5] There is good evidence to support the use of cyclosporine in antihistamine refractory chronic urticaria and guidelines also recommend its use as third-line therapy; but its problematic adverse effect profile and cost can, on occasion, limit its clinical utility.[1]

Methotrexate was first synthesized by Yellapragada Subbarao, an Indian-American Harvard graduate from Andhra Pradesh.[6] The first reported use of methotrexate in chronic urticaria was by Weiner in 1989; he successfully achieved complete remission with methotrexate in a patient with chronic, steroid-dependent, recalcitrant urticaria.[7] Methotrexate may be an affordable, easily available and well-tolerated alternative to achieve remission in refractory chronic urticaria; its effect in chronic urticaria is through its effect on adenosine and inhibition cytokines, oxidative burst and leukocyte chemotaxis.[8]

The current recommendation in urticaria does not detail the dose and duration for methotrexate. There is a paucity of systematic reviews devoted to evaluation of the use of methotrexate in chronic urticaria. Hence, the aim of this study was to systematically review the use/efficacy of methotrexate in chronic urticaria.

Methods

This systematic review was done following Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) recommendations.[9]

Data sourcing

This systematic review was conducted in the Department of Dermatology, Dayanand Medical College and Hospital, Ludhiana (Punjab). Two investigators (J.S.and A.K.) independently conducted a systematic search in four databases, that is, PubMed/Medline, Cochrane Central, Google Scholar and Clinicaltrials.gov on April 6, 2020, using keywords "methotrexate [MeSH terms]" AND "urticaria" OR "urticaria, chronic" OR "urticaria, chronic spontaneous."

Data extraction

A total number of items found on search were 6188 (741–Google Scholar, 4959 –PubMed/Medline, 485 – Cochrane Central and 3 – www.clinical trials.gov) [Figure 1].

Selection criteria/eligibility

Articles were screened by title and abstract. The articles included were randomized control trials, case–control studies, prospective intervention studies, retrospective reviews, case series and case reports. Descriptive reviews, guidelines and expert opinions were excluded. Both the investigators independently assessed the articles for their eligibility. After

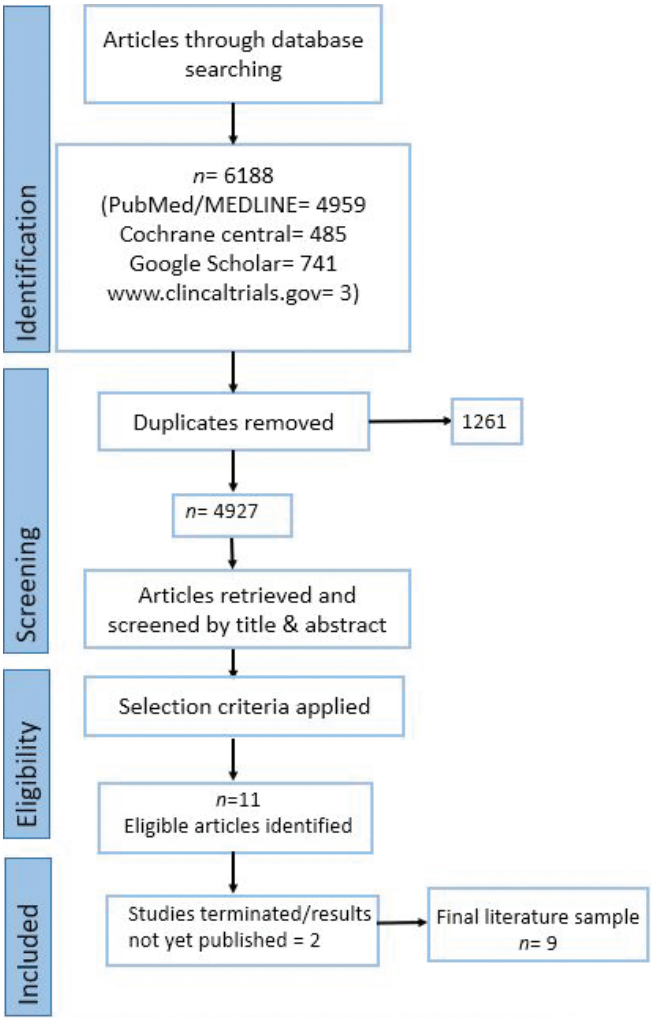

Figure 1: Flow diagram and literature review

removing duplicates and applying the selection criteria, we obtained nine articles [Figure 1]. The full text of the selected literature was studied by both the investigators independently. A detailed proforma was prepared by the investigators wherein following data from the available literature were tabulated– study type, mean age, gender ratio, sample size, type of urticaria, disease duration, inclusion criteria, treatment protocol, tool(s) used for assessment of response, side effects and follow-up.

Bias assessment

Quality and bias of the included studies were assessed using the Oxford Quality Scoring System for the randomized control trials and methodological index for non-randomized control trials for the rest.[10,11]

Outcome analysis

The level of evidence on the efficacy of methotrexate in chronic urticaria was assessed by a numerical scale– the Copenhagen Evidential Scale of Treatments introduced by Holm *et al*., based on parameters including study design, number of studies, study participants and treatment efficacy [Table 1].[12]

Table 1: Copenhagen evidential scale of treatments(Adapted from Holm *et al*.)[12]

Parameters	Level of evidence (points)	Specification for calculation
Study design		
Randomized controlled trial	3	Each study scored (mean acrossstudies used)
Prospective intervention	2	
Caseseries	1	
Single-casereport	0	
Number of studies identified		
10<–Strong evidence	2	Each treatment scored
5<×≤10–Intermediate evidence	1	
5≤–Weak evidence	0	
Number of patients treated		
50<	2	Number of patients treated in total
20<×≤50	1	
≤20	0	
Effect of treatment		
↑↑↑	3	Average across all patients treated (total score/number of patients). Studies without exact measures or indicative of variations in efficacy will not be included and the patients cut from the equation
↑↑	2	
↑	1	
→	0	
↓	–1	
Total score(maximum of 10 points)	7≤-A	A – Very strong evidence
	5.5≤×<7-B	B – Strong evidence
	4.5≤×<5.5-C	C–Intermediate evidence
	3≤×<4.5-D	D – Weak evidence
	<3-C	E–Very weak evidence

Results

The nine selected articles included three randomized control trials, one uncontrolled prospective interventional trial, three retrospective reviews and two case reports. The quality and risk of bias of selected articles are presented in Table 2.

Patient selection criteria/profile

The total number of patients in all the studies included were 127(*n*). The age of the patients across the studies varied from 15 to 75 years. Female predominance was seen in most of the studies. The disease duration of the patients varied from few weeks up to 24 years. The study population (*n=127*) included 93 patients with chronic urticaria, 21 with chronic urticaria (steroid-dependent), 11 with chronic autoimmune urticaria and two angioedema [Table 3].

The patients included in various studies, often did not respond to first- and second-generation antihistamine therapy and were subsequently put on second-/third-line immunosuppressive agents. Some even needed injectable (subcutaneous) adrenaline and corticosteroids (hydrocortisone) for severe, acute flares [Table 4].

Treatment protocol

Methotrexate was used in variable doses in different studies, the maximum dose being 25mg/week [Table 5]. The route of administration was oral for all patients except two patients who could not tolerate oral methotrexate due to gastrointestinal side effects. Methotrexate was administered as a once weekly dose in all studies except in cases reports by Weiner, Montero *et al*. and Godse who gave methotrexate for two–three days/week.[7,13,14] The duration of treatment varied from few weeks to over six months [Table 5].

Response to treatment

The outcome measures varied across different studies [Table 5]. In a randomized control trial conducted by Leducq *et al*. on antihistamine-refractory urticaria, the outcome measures were based on the reduction of urticarial wheals and decrease in the intensity of pruritus with methotrexate. They chose a stringent criterion for response to treatment, that is, complete remission was defined as no new lesions within 30 days of stopping treatment. In their study, with 39 cases and 36 controls, respectively, three cases achieved complete remission with methotrexate whereas none of the placebo group had complete remission while 11 cases on methotrexate and six from placebo group had partial remission.[15] Both Sharma *et al*. and Yadav *et al*. measured outcomes using urticaria severity assessment, which included scoring the number, size, frequency and duration of wheals as well as severity of pruritus.[16-18]

In a placebo-controlled randomized control trial conducted by Sharma *et al*., with 14 cases and 15 controls, there was significant improvement in urticaria severity assessment score in the methotrexate group; however, no additional

Table 2: Risk of bias assesment for the included studies

(a) Quality and risk of bias assessment of included RCTs[10]

	Randomization	Randomization scheme	Double blinded	Blinding scheme	Dropouts/ withdrawals
Leducq *et al*., 2020[15]	√	√	√	√	√
Yadav *et al*., 2017[16]	√	-		-	-
Sharma *et al*., 2013[17]	√	-	√	√	√

(b) Quality and risk of bias assessment of included non-RCTs[11]

	A stated aim of the study	Inclusion of consecutive patients	Prospective collection of data	End point appropriate to the study aim	Unbiased evaluation of end points	Follow-up period appropriate	Loss to follow- up not exceeding 5%
Mora *et al*., 2004 [13]	2	2	2	2	0	0	2
Perez *et al*., 2009[20]	2	0	0	1	0	0	0
Sagi *et al*., 2011[19]	0	0	0	0	0	0	0
Godse, 2004[21]	0	0	0	0	0	0	0

	Prospective calculation of the study size	A control group having the criterion standard intervention	Contemporary groups	Baseline equivalence of groups	Prospective calculation of the sample size	Statistical analyses adapted to the study design	Total
Mora *et al*., 2004 [13]	0	0	0	0	0	2	12
Perez *et al*., 2009[20]	0	0	0	0	0	1	4
Sagi *et al*., 2011[19]	0	0	0	0	0	0	0
Godse, 2004[21]	0	0	0	0	0	0	0

benefits over antihistamines were seen (urticaria severity assessment score; pruritus and wheal score, $P = 0.923$ and 0.929, respectively).[17] Similarly, in a randomized control trial conducted by Yadav *et al*. with 40 cases and controls each, they concluded that though both groups showed a significant improvement in all parameters of urticaria severity assessment score; there was no statistically significant difference between the methotrexate and placebo groups (urticaria severity assessment score, pruritus/wheal score, $P>0.05$).[16]

Sagi *et al*., in a retrospective review, reported good response to methotrexate in eight patients with steroid-dependent chronic urticaria. They reported that 87% of patients had complete remission with methotrexate at 15–25 mg/week.[19] Doses of steroids could be gradually tapered.

Perez *et al*. reported on the benefits of methotrexate in patients with steroid-dependent chronic urticaria with gradual reduction in steroid doses. Among 12 patients, reviewed retrospectively, 16.7% showed complete clearance of urticaria, 58% had considerable benefit and 25% of patients showed some benefit after methotrexateuse.[20]

Montero *et al*. conducted a prospective interventional study on seven patients with chronic urticaria. They reported benefit in all the seven patients by the end of six weeks with significant improvement in itching and wheal score ($P= 0.003$ and 0.004, respectively).[14]

Godse also reported a case series of four patients with recalcitrant autoimmune urticaria who had a positive autologous serum skin test. He observed marked improvement with methotrexate.[14] Gach *et al*. and Weiner also reported cases with good response to methotrexate.[7,21]

Tests for functional antibodies (i.e.,autologous serum skin testand basophil histamine release assay} were done in a few studies; however,no significant correlation was seen between presence of functional antibodies and response to methotrexate [Table 6].[14,20]

Quality of life

Leducq *et al*. reported improvement in dermatology life quality index from baseline to week 18 in both groups which was not statistically significant ($P=0.57$).[15] However, Montero reported statistically significant improvement in impact on daily activity at the end of six weeks with methotrexate ($P= 0.003$).[13]

Table 3: Demographic and clinical profile of the study participants (*n*=127)

Author	Study design	Age mean/range	Male:female ratio	Type of urticaria	Mean duration of urticaria
Leducq *et al*.,2020[15]	RCT	46.4	11:28	CSU=39	4.9 yrs.
Yadav *et al*.,2017[16]	RCT	35.33±4.53 yrs. (mean)	17:23	CU=40	1.8 yrs.
Sharma *et al*., 2013[17]	RCT	34.21 ±10.42 yrs. (mean)	6:8	CSU=14	1.9 yrs.
Sagi *et al*.,2011[19]	Retrospective review	54±19/(18–74 yrs.)	2:6	Steroid-dependent CU=8	12 ± 8 mo.
Perez *et al*.,*2009[20]	Retrospective review	49yrs/(30–75 yrs.)	3:9	Steroid-dependent CU=10 Angioedema=2	48.5 mo.
Godse, 2004[14]	Case series	15–55 yrs.	3:1	CAU=4	NR
Mora *et al*., 2004[13]	Uncontrolled Prospective,interventional trial	NR	2:5	CAU=7	NR
Gach *et al*., 2001[21]	Case report	Case1=42 yrs. Case 2= 37 yrs.	1:1	Steroid-dependent CIU + Angioedema	Case 1=intermittent episodes since childhood Case 2=8 mo.
Weiner, 1989[7]	Case report	48 yrs.	1 male	Steroid-dependent CU	24 yrs.

*12 patients with chronic urticaria and angioedema were included in our review; four patients with urticarial vasculitis were excluded from this analysis. NR: Not reported by author, CU: Chronic urticaria, CSU: Chronic spontaneous urticaria, CAU: Chronic autoimmune urticaria, RCT: Randomized controlled trial, yrs.: Years, mo: Months

Adverse effects

In the largest randomized control trial with 75 cases conducted by Leducq *et al*., a number of side effects were reported. These included gastrointestinal side effects, deranged LFTs, bone marrow depression, nasopharyngitis and asthenia among others.[15]Among other reviewed studies, only minor side effects were observed; only one patient had uncontrolled nausea and vomiting due to methotrexate given at 15mg/week dose following which it had to be withdrawn [Table 3].

Clinical outcome, follow-up and relapse

Complete remission, seen in three patients (methotrexate group), was defined as no urticarial lesions within the 30 days; partial remission, seen in 11 cases (methotrexate group), was defined as <7 days of urticarial lesions within 30 days before the 18-week end point by Leducq *et al*. Treatment with methotrexate was discontinued after 18 weeks and patients were followed up till 26 weeks.[15]

Sharma *et al*. followed up ten of their patients; at the end of six months follow-up, one patient (methotrexate group) had complete remission, that is, no lesions without antihistamines, two had partial remission, that is, reduction in antihistamine dose (one from each group), while the rest had relapsed immediately after stoppage of therapy.[17]

Sagi *et al*. followed up patients up to ten months (range 1-10 months), 71.4% (5/7) achieved complete remission after stopping methotrexate (i.e. no lesions after stopping treatment), while two patients were still on methotrexate at the time of analysis.[19]

Godse *et al*. noted that one patient out of four relapsed two weeks after stopping methotrexate.[14] Weiner reported a relapse at six months post-methotrexate and the drug had to be restarted.[7]

Evidence for methotrexate use

After evaluating the articles, the evidence for methotrexate use was calculated with the Copenhagen evidential scale of treatments; the score obtained for methotrexate using selected literature was 6.7.[12] As per the scale, this score is considered as strong evidence (B)[Tables1 and 7].

Discussion

On our literature search, there were limited articles on methotrexate use in chronic urticaria, majority being retrospective reviews and case series. The total participants in all the studies included were 127. Till date, only three randomized control trials (n=93) have been published and there is considerable heterogeneity in their methods. Therefore, due to the small number of studies of limited quality, a meta-analysis could not be done [Table 2a].

The largest and highest quality randomized control trial in our review was by Leducq *et al*., which included 39 cases and 36 controls; however, they chose an arbitrary measure for treatment response which did not compare well with other randomized control trials. Since they chose a stringent criterion for the treatment response, only three patients achieved complete remission in the methotrexate group. Although no dropouts were reported, the total number of patients finally recruited in the two groups were less than the initially proposed sample size of 110.[15]A treatment goal with a stringent criterion of no lesion in the past 30 days is perhaps too ambitious for any therapeutic modality. In real life, unless a motivated patient keeps a symptom diary, this may neither be accurate nor feasible. This is precisely why that with a less stringent criterion (i.e., partial remission–no lesions in the past 14 days), 14 patients reported benefits with methotrexate. Sharma *et al*. reported no additional benefit of methotrexate over antihistamines alone. The dropout rate was also high with 28.6% and 53.3% for cases and controls,

Table 4: Selection criteria/clinical profile of patients in various studies

Author	Patient selection/clinical profile	Therapeutic agents given before MTX
Leducq *et al*., 2020[15]	1. CU treated with threedifferent anti-H1 molecules or 2. Combination of twodifferent anti-H1 molecules or 3.One anti-H1 molecule used at double dose for ≥3 months 4. With persistency of at least sevendays with urticarial lesions in the previous month	Antihistamines† Multiple Leukotriene inhibitor Montelukast Corticosteroid Oral Others Colchicine
Yadav *et al*., 2017[16]	Patients with chronic spontaneous urticaria.	NR
Sharma *et al*., 2013[17]	Antihistamine-resistant chronic spontaneous urticaria was defined as less than 50% reduction in urticaria activity score (UAS) with: Five milligrams of levocetirizine or tenmilligramscetirizine BD for 15 days + Combination of fexofenadine 180 mg and hydroxyzine 25 mg for another 15 days	Antihistamines Levocetirizine Cetirizine Fexofenadine Hydroxyzine
Sagi *et al*., 2011[19]	Patient with steroid-dependent chronic urticaria (biopsy performed)	Antihistamines* Corticosteroid Oral prednisolone (30–40 mg/day) Intravenous hydrocortisone Others Doxepin Colchicine Dapsone
Perez *et al*., 2009[20]	Patients with steroid dependent, recalcitrant chronic urticaria	Antihistamines* Second generation Corticosteroid Oral prednisolone (10–60 mg/day) Leukotriene inhibitor Montelukast Immunomodulator Azathioprine Ciclosporin Others Colchicine Hydroxychloroquine Sulfasalazine Dapsone, Doxepin I/v immunoglobulins
Godse,2004[14]	Patient with recalcitrant CU + positive ASST	Antihistamines Fexofenadine Cetirizine Hydroxyzine
Mora *et al*., 2004[13]	Patients with chronic autoimmune urticaria with positive ASST	Antihistamines Hydroxyzine Montelukast Desloratadine
Author	Patient selection/clinical profile	Therapeutic agents given prior to MTX
Gach *et al*., 2001[21]	Case 1: CU + angioedema, arthralgia, myalgia, eye soreness, breathlessness, arthritis; negative ASST. Challenge test for delayed pressure urticaria was positive(biopsy performed) Case 2:CU + angioedema, negative ASST. Challenge test for delayed pressure urticaria was positive. Cushingoid features, adrenal insufficiency seen	Antihistamines Chlorpheniramine Astemizole Fexofenadine Acrivastine Corticosteroid Oral prednisolone (40–60 mg/day) Immunomodulator Ciclosporin Others Doxepin Dapsone Adrenaline Ephedrine spray
Weiner, 1989[7]	Patient with chronic urticaria + angioedema, high fevers, arthralgias, arthritis	Antihistamines Cyproheptadine Corticosteroid Subcutaneous hydrocortisone Others Adrenaline

*Details of antihistamines not reported in published article, NR: Not reported

Table 5: Summary of treatment protocol, efficacy, follow-up and adverse effects in the various studies

Author	Cases	Controls	Treatment protocol	MTX Dose	Duration of treatment	Response*	Follow-up and dropout	Adverse effects
Leducq *et al*., 2020[15]	39	36	MTX +antihistamines;Placebo +antihistamines	0.2 mg/kg/wk. (↑ by 0.25mg/ kg/wk., if no response)	18 weeks	3×↑↑↑ 11×↑↑	ND dropout – none	17 had gastrointestinal symptoms
Yadav *et al*., 2017[16]	40	40	MTX;Placebo	15 mg/ week	8–12 weeks	40×↑↑	ND dropout– none	NR
Sharma *et al*., 2013[17]	14	15	MTX + levocetirizine 5 mg daily Placebo + levocetirizine 5 mg daily	15 mg/week	12 weeks	1×↑↑↑ 2×↑↑	3.5±2.4 months Dropout=12 (fourcases, eightcontrols)	Uncontrollable nausea,vomiting=1(withdrew from study)raised transaminase level-2
Sagi *et al*., 2/011[19]	8	NA	MTX + antihistamines+ 5 mg folic acid once weekly(steroid tapered gradually)	15mg/week (non-responder: up to 25 mg/week)	4.5±3 months	7×↑↑↑ 1×→	8.25±4.6months Dropouts–NA	GI intolerance=2 Raised LFT=1 Weakness =1
Perez *et al*., 2009[20]	12†	NA	MTX + antihistamines+ 5 mg folic acid once weekly(steroid tapered gradually)	10–15 mg/week (non-responder: up to 25 mg/week)	Variable§	1×↑↑↑ 5×↑↑ 3×↑ 3×→	ND Dropouts– NA	Hair thinning and fatigue
Godse, 2004[14]	4	NA	MTX + antihistamines+1.5 mg folic acid daily	10mg/week in divided doses	8 weeks	4×↑↑	One relapse after two weeks of stopping MTX	NR
Mora *et al*., 2004[13]	7	NA	MTX	10–15mg/week in divided doses	6 weeks	6×↑↑↑ 1×↑↑	ND	Headache and nausea
Gach *et al*., 2001[21]	2	NA	Case1=MTX +antihistamines(oral cyclosporine tapered and stopped) Case 2=MTX + antihistamines (oral steroids tapered off gradually)	15mg/week 20mg/week	NR NR	2×↑↑	ND	NR
Weiner, 1989[7]	1	NA	MTX(oral steroids tapered off gradually)	15mg/week in divided doses	NR	1×↑↑↑	Relapse after sixmonths MTX again started	Slight elevation in SGPT/ SGOT Mild leukopenia

*Effects of treatment as per CEST (Copenhagen evidential scale of treatments). †Twelvepatients with chronic urticaria and angioedema were included in our review; four patients with urticarial vasculitis were excluded from this analysis. §Patients were given cumulative dose of 174.7 mg MTX, duration varying from three weeks to >six months. MTX: Methotrexate, CYA: Cyclosporine A, ND: Not done, N/A: Not applicable, NR: Not reported, SGOT: Serum glutamic oxaloacetic transaminase, SGPT: Serum glutamic pyruvate transaminase

Table 6: Functional antibody results done in various studies

Author	ASST		BHRA		Remarks
	+ve	–ve	+ve	–ve	
Sharma *et al*., 2013[17]					ASST negative (with MTX):
Case=10	7	3	ND	ND	Mean wheal scores: ↓ in 30% patients
Control=7	3	4	ND	ND	Mean pruritus scores: ↓ in 40% patients ASST positive (with MTX): Mean wheal scores: ↓ in 14.2% patients Mean pruritus scores: ↓ in 28.4% patients In the placebo group, the ASST-positive group showed a better response.
Perez *et al*., 2009[20] *n*=12(threeout of 12 patients not tested)	4	2	2	2	Five patients with considerable benefit (i.e.,↓ wheals, symptoms, ↓ steroid dose), one had -ve ASST andBHRA, while one had -ve BHRA(ASST=ND), one was +ve for ASST (BHRA=ND) and the rest were not tested In threepatients with no benefit on MTX, twohad +veASST while one had not been tested
Mora *et al*. 2004[13] *n*=7	7	nil	ND	ND	ASST was positive in the sevenpatients included in the study At the end of sixweeks, good response was seen in all of the patients with methotrexate
Godse, 2004[14] *n*=4	4	nil	ND	ND	In antihistamine-resistant CAU patients, there was marked improvement after treatment for onemonth
Gach *et al*., 2001[21] *n*=2	0	2	nil	2	Good response in steroid-dependent cases who had developed adrenal insufficiency andCushingoid features due to chronic steroid use

ASST: Autologous serum skin test, BHRA: Basophil histamine release assay, MTX: Methotrexate, ND: Not done, CAU: Chronic autoimmune urticarial

respectively. One patient withdrew early from the study due to uncontrolled nausea and vomiting.[17]

In terms of selection criteria, Leducq *et al*. included patients who had received multiple anti-H1 molecules or a single anti-H1 molecule at double dose for more ≥ three months. Some even received immunosuppressants and leukotriene inhibitors. Thus, their patient population had more chronic, severe and recalcitrant course. In comparison, Sharma *et al*. gave a shorter course with no reported history of immunosuppressants.[15,17] The authors opine that the difference in their response to methotrexate could be attributed to this fact.

The randomized control trial by Yadav *et al*. had no defined patient selection criteria. Furthermore, there was no documentation of dropouts or follow-up of patients for relapse.[16] Hence, the finding reported by them should be taken with a grain of salt.

Good results have been reported with methotrexate in steroid-dependent chronic urticaria in retrospective reviews and anecdotal case reports.[19-21]

Sagi *et al*. and Perez *et al*. up-dosed methotrexate for non-responders up to 25mg/week, which may have contributed to better response compared to other studies where lower doses were given.[19,20] In this review, 20 patients included were steroid-dependent cases; it appears that in these patients, methotrexate is beneficial especially at higher doses.[19-21]

Various authors have suggested that chronic spontaneous urticaria may be an autoimmune condition in a substantial proportion of cases.[22] Autologous serum skin test was done to investigate for autoimmune urticaria in studies by Sharma *et al*. and Perez *et al*.[17,20] However, response rate to methotrexate was not influenced by autologous serum skin test results. Since we expect methotrexate to alter the level of functional antibodies, larger studies may be done in the future to further investigate its role in autoimmune urticaria.

Methotrexate is a relatively safe drug when used at lower doses for dermatological diseases with very few adverse effects; severe adverse drug reaction (bone marrow depression and pulmonary fibrosis) is generally not seen in the doses used for urticaria. Severe gastrointestinal symptoms usually presented early in the course of treatment and were easily identified and managed.[17] Parenteral route is an option for patients who do not tolerate the drug orally [Table 8].

Cyclosporine is another effective and commonly used drug in recalcitrant cases, but its side effects can be troublesome. In a meta-analysis by Kulthanan *et al*., cyclosporine was found to be an effective modality to treat urticaria in low-to-moderate doses; though, adverse events were seen in patients receiving moderate doses (4–5mg/kg/day) of cyclosporine (elevated creatinine, hypertension, headache, hirsutism, infections and paresthesia).[23] Although methotrexate scores over cyclosporine in terms of safety and cost; the question of its efficacy is still subject to the availability of more scientific evidence.

Omalizumab has drastically altered treatment paradigms for chronic urticaria patients, wherein a few injections can lead to a potential cure. In a meta-analysis conducted by Zhao *et al*., it was seen that omalizumab was significantly more effective in reducing weekly wheal score and weekly itch score as compared to placebo. It also showed complete resolution (i.e. a post-treatment UAS7 score of 0) in 36% of patients at 300mg dosing.[5] However, it may not be a silver bullet in all cases; being a chimeric monoclonal antibody, there remains a risk of immunological reactions.[24,25] Although

Table 7: Application of Copenhagen evidential scale of treatments to the findings of present systematic review[12]

Scale parameters	Factor	Findings of present systematic review	Score	Mean	
Study design					
Randomized controlled trial	3	3	9	14/9	1.6
Prospective intervention	2	1	2		
Caseseries	1	3	3		
Single-casereport	0	2	0		
No. of studies identified	-	9	1	-	1
No. of patients treated	-	127	2	-	2
Effect of treatment*					
↑↑↑	3	19	57	190/91	
↑↑	2	65	130		
↑	1	3	3		
→	0	4	0		
↓	-1	0	0		
Total					6.7

*Treatment response was clearly mentioned for 91 cases out of 127 in the studies reviewed

Table 8: Common side effects of methotrexate

System	Side effect
Gastrointestinal	Nausea Vomiting Diarrhea Anorexia Ulcerative stomatitis
Hepatic	Transaminitis Cirrhosis
Hematological	Thrombocytopenia Neutropenia Pancytopenia Myelosuppression
Pulmonary	Acute pneumonitis Pulmonary fibrosis
Reproductive	Teratogenicity Abortifacient
Renal	Renal papillary necrosis
Others	Alopecia Headache Fatigue Risk of malignancy

a highly effective alternative in refectory cases of urticaria; its high-cost limits use in developing nations where health insurance coverage may not be universal.

Recently, a systematic review of the effects of add-on methotrexate has been reported by Patil *et al*.; they concluded that though well tolerated, there may be no add-on benefit of methotrexate in difficult to treat urticaria with the caveat that this recommendation is based on limited data.[26]

Current Indian guidelines still recommend methotrexate, even with the paucity of good evidence, due to its suitability from the Indian perspective with respect to cost, availability, dosing schedule and good acceptance.[27]

On reviewing the available literature, we concur that application of methotrexate may be limited to cases where antihistamines have failed or the patient may have become steroid-dependent. Although omalizumab has considerably better efficacy in many of these cases, nonetheless methotrexate is still an additional tool in the dermatologist's armamentarium. Cyclosporine, with good efficacy and reasonable safety, is another popular alternative; however, no randomized control trials to compare cyclosporine with methotrexate are currently available. The limitation of our study is that due to the paucity of literature, a meta-analysis could not be performed.

Conclusion

We conclude that all patients may not be good candidates for methotrexate; more evidence from as larger, well-executed randomized control trials is needed in order to give more definitive answers. Patients with prolonged disease course, not responding to multiple antihistamines, and steroid-dependent cases may be the potential candidates where methotrexate may prove useful.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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