Original Research Article

Methotrexate therapy in chronic idiopathic urticaria with negative autologous serum skin test

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Abstract

Background: Chronic urticaria is a relatively common disorder that can be severe and may impair quality of life. The management of recalcitrant chronic urticaria that is not responding to histamine antagonists includes short-term systemic corticosteroids, anti-inflammatory drugs and immunomodulatory agents, such as cyclosporine, methotrexate, plasmapheresis and intravenous immunoglobulin. In this study we treated patients of chronic urticaria with ASST negative to see the effect of methotrexate therapy. **Aim and Objective:** to study the effect of methotrexate therapy in chronic idiopathic Urticaria with negative Autologous Serum Skin Test **Methodology:** Total 60 patients with history of urticaria for more than 6 weeks were studied. ASST was done. ASST negative patients were studied. Methotrexate therapy was started and data was collected regarding effect of this drug. **Results and Discussion:** The mean UAS in ASST negative patients at baseline was 4.9 and at 8 weeks was 0.4.The mean frequency of attacks in ASST negative at baseline was 9.9 and at 8 weeks was 2.75. The mean frequency of antihistamine drugs taken in ASST negative patients was 2.62 at baseline and 0.32 at 8 weeks. The difference in values at baseline and at 8 weeks of all the three parameters – UAS, frequency of attacks and frequency of antihistamine drug taken was statistically significant.
Key Words: Methotrexate therapy.

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INTRODUCTION

Urticaria is defined as 'acute' if it lasts for less than 6 weeks and' chronic' if it lasts for more than 6 weeks. 'Episodic' urticaria, which occurs intermittently, but recurrently overmonths or years, is also recognized. Urticaria lasting greater than 6 weeks is divided into 2 general groups i.e. inducible and chronic spontaneous urticaria (CSU).[1] Inducible urticarias are intermittent urticarias because the frequency is dependent on the particular stimulus. In this category are physical urticarias *e.g.*, cold urticaria and dermatographism.[2] Others include local heat urticaria, generalized heat urticaria (more commonly called cholinergic urticaria), solar urticaria, and aquagenic urticaria. The second major category is CSU. Lesions appear unpredictably, are present most days of the week, can occur on virtually any part of the body, are associated with angioedema (but not laryngeal edema) in 40% of patients, and respond to corticosteroids. The treatment of chronic spontaneous urticaria begins with antihistamines; however, the dose required typically exceeds that recommended for allergic rhinitis. Second-generation, relatively non-sedating H1-receptor blockers are typically employed up to 4 times a day. First-generation antihistamines, such as hydroxyzine or diphenhydramine (Atarax or Benadryl), were employed similarly in the past. Immunosuppressive therapies when routine treatment fail to show control of urticaria. The beneficial effects of methotrexate are anti inflammatory and immunosuppressive. It is beneficial in chronic urticaria independently of the pathogenic mechanism,

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whether autoimmune or not with minimal side effects. This study was conducted to see the effect of methotrexate in ASST negative patients in chronic urticaria.

MATERIAL AND METHODS

The study was conducted on Patients above 18 years having urticaria for more than 6 weeks with no identified cause attending the outpatient department of Dermatology of a tertiary care centre.

Inclusion Criteria

1. Patients above the age of 18yrs
2. Patients having daily or almost daily episodes of urticarial wheals > 6 weeks
3. Patient is willing to be part of study after informed consent

Exclusion Criteria

1. Patients having physical urticaria.
2. Patients having food allergy and urticaria of known cause.
3. Patients having positive ANA test.
4. Patients having raised serum IgE levels.
5. Pregnant women and lactating mothers.
6. Immunocompromised patients 7. Patients on immunosuppressive drugs.

Total 60 patients were studied after applying inclusion and exclusion criteria. The study design was approved by the Institutional Ethics Review Committee (IERC). A valid Written informed consent was obtained from patients after explaining study to them. Data was collected using detailed questionnaire. It included detailed history, clinical examination and investigations like ASST test, complete blood count, ESR, blood sugar tests, liver function tests, renal function tests, serum IgE levels, thyroid function tests and ANA. 0.05ml of both autologous serum and 0.9% normal saline were separately injected intradermally in to volar aspect of left forearm with a distance of 5 cm apart. Wheal and flare response was measured at the end of 30 minutes. ASST was considered to be negative if a serum induced wheal was not bigger than the saline induced response by > 1.5 mm seen at the end of 30 minutes[3]. A test dose of tablet methotrexate of 2.5mg was given first to every patient and complete blood count was repeated after 7 days. If the blood counts were normal patient was started on methotrexate therapy. Methotrexate was given in the dose of 5mg BD weekly for 8 weeks and on remaining six days folic acid 5mg OD was given to all patients. The patients were assessed at 2, 4, 6 weeks after starting treatment and at 8 weeks after completion of treatment. Data was analysed using appropriate statistical tests.

RESULTS

Out of 60 patients, 40 patients (66.7%) were ASST negative and out of 60 patients 20 patients (33.3%) were ASST positive. In negative ASST group there were 17 (42.5%) females and 23 (57.5%) males out of 40 negative ASST patients

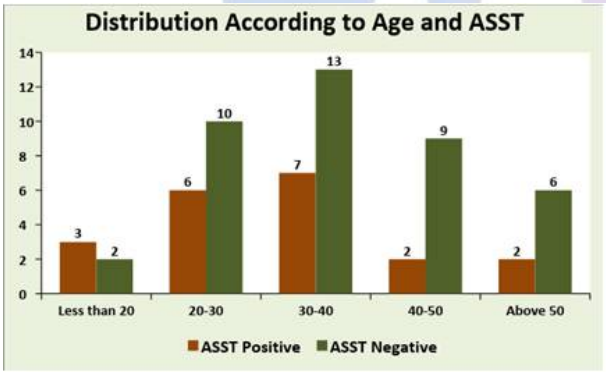

Figure 1

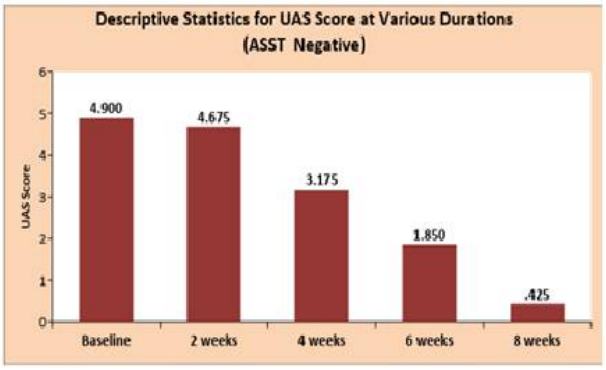

Figure 2

Figure 1: Distribution of patients according to age and ASST; **Figure 2:** Descriptive statistics for USA score at various durations in ASST negative patients.

The maximum number of patients with negative ASST, 13 (12.67%) out of 40 were in 30 years to 40 years age group followed by 10 (16.67%) in 20 years to 30 years age group,9 (15%) in 40 years to 50 years age group,(fig 1) In our study the mean value of urticaria activity score (UAS) at baseline in ASST negative patients was 4.90 (SD ± 1.21). The mean frequency of attacks in patients with negative ASST at baseline was 9.9 (SD ± 3.44). The mean frequency of antihistaminic drugs taken in ASST negative patients at baseline was 2.62 (SD ± 0.97). The mean UAS in ASST negative patients at baseline was 4.9 (SD ± 1.215), at 2 weeks was 4.67 (SD ± 1.185), at 4 weeks was 3.17 (SD ± 1.174), at 6 weeks was 1.85 (SD ± 1.167) and at 8 weeks was 0.42 (SD ± 0.636) respectively. There was statistically significant difference in the mean value of UAS at baseline and at 8 weeks in ASST negative patients using ANOVA test ($p< 0.001$).

Table 1: Descriptive Statistics for Frequency of Attacks (ASST Negative)

Duration	ASST	Mean	SD	N	p-value	Significance
Baseline	Negative	9.90	3.448	40	< 0.001	Significant at 1% level
2 Weeks	Negative	10.00	3.419	40		
4 Weeks	Negative	6.80	2.514	40		
6 Weeks	Negative	5.33	2.165	40		
8 Weeks	Negative	2.75	2.994	40		

The mean value of frequency of attacks in ASST negative patients at baseline was 9.90 (SD ± 3.44), at 2 weeks was 10.0 (SD ± 3.41), at 4 weeks was 6.8 (SD ± 2.51), at 6 weeks was 5.33 (SD ± 2.16) and at 8 weeks was 2.75 (SD ± 2.99) respectively. There was statistically significant difference in the mean value of frequency of attacks in ASST positive patients at baseline and at 8 weeks duration using ANOVA test (p< 0.001).(table 1).

Table 2: Mean Frequency Antihistaminic Drug Taken at Various Durations (ASST Negative)

Antihistaminic taken at	ASST	Mean	SD	N	p-value	Significance
Baseline	Negative	2.625	0.97895	40	< 0.001	Significant at 1% level
2 Weeks	Negative	2.5	0.84732	40		
4 Weeks	Negative	1.75	0.58835	40		
6 Weeks	Negative	1.45	0.74936	40		
8 Weeks	Negative	0.325	0.69384	40		

Also, the mean frequency of antihistaminic drugs taken in ASST negative patients at baseline was 2.625 (SD ± 0.97), at 2 weeks was 2.5 (SD ± 0.84), at 4 weeks was 1.75 (SD ± 0.58), at 6 weeks was 1.45 (SD ± 0.74) and at 8 weeks was 0.325 (SD ± 0.69) respectively. The difference in the mean value of frequency of antihistaminic drugs taken in ASST negative patients at baseline and at 8 weeks was statistically significant using ANOVA test (p<0.001).(Table 2).

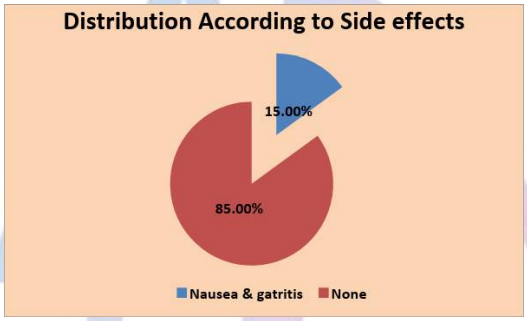

Figure 3: Distribution of patients according to side effects

In our study, side effects were seen in 9 (15%) out 60 patients and were minimal in the form of nausea and gastritis in the initial period and there was no dropout of patients due to side effects.

DISCUSSION

Various studies have demonstrated IgG autoantibodies against IgE and / or FcεRIa in the serum ofsome patients with CIU[4,5].Although their clinical significance is still unclear, FcεRIa autoantibodies havebeen demonstrated in about one-third of patients withchronic urticaria. Furthermore, in some cases of CIU intradermal injection of autologous serum can cause a wheal and flare response[6]. The present study has evaluated 60 patients with chronic idiopathic urticaria (CIU) by autologous serum skin testing. All the patients were given Methotrexate therapy with a dose of 5 mg tablet BD once in a week and Folic acid tablet 5 mg was given on remaining 6 days. The patients were then assessed for response at the end of 2, 4, 6 and 8 weeks. Response was assessed according to the change in Urticaria Activity Score (UAS), frequency of attacks and frequency of antihistaminic drug taken at every visit. The efficacy of methotrexate was assessed by comparing the values of UAS, frequency of attacks and frequency of antihistaminic drug taken at baseline and at 8 weeks. The efficacy was assessed in negative ASST group. The compliance of the patients was good and there were no drop outs. In our study, the difference in the mean urticaria activity score (UAS) at baseline and at 8 weeks was statistically highly significant (p<0.001). There was decline in the UAS with the duration thus proving efficacy of methotrexate. The mean UAS in ASST negative patients at baseline was 4.9, at 2 weeks 4.67, at 4 weeks 3.17, at 6 weeks 1.85 and at 8 weeks was 0.42 respectively. There was statistically significant difference in the mean value of UAS at baseline and at 8 weeks in ASST negative patients (p< 0.001). The mean value of frequency of attacks in ASST negative patients at baseline was 9.90, at 2 weeks 10.0, at 4 weeks 6.8, at 6 weeks 5.33 and at 8 weeks it was 2.75 respectively. There

was statistically significant difference in the mean value of frequency of attacks in ASST negative patients at baseline and at 8 weeks duration ($p< 0.001$). The mean frequency of antihistaminic drugs taken in ASST negative patients at baseline was 2.625, at 2 weeks 2.5, at 4 weeks 1.75, at 6 weeks 1.45 and at 8 weeks was 0.325 respectively. The difference in the mean value of frequency of antihistaminic drugs taken in ASST negative patients at baseline and at 8 weeks was statistically significant ($p<0.001$). Gach E *et al* in 2001 reported two patients with no detectable antibodies having antihistamine-resistant, corticosteroid dependent CIU who responded to methotrexate therapy with a dose of 15 mg/week[3]. Both the patients mentioned in the study were first treated with cyclosporine 200mg; no improvement was seen in first patient while cyclosporine was discontinued in second patient because of the side effects.They proposed that the effects of methotrexate on neutrophil adhesion and accumulation and leukotriene synthesis, may be relevant to chronic urticaria rather than immunosuppression. In one study conducted by Perez A *et al* in 2010 found methotrexate therapy with a dose of 10-15 mg/ week effective in 12 out of 16 patients of chronic urticaria. In the mentioned study, four of eight responders and three out of three non -responders showed evidence of functional autoantibodies. Response to methotrexate was assessed by reduction in number of wheals and reduction of steroid dose[7] Sagi L *et al* in 2011 reported a retrospective findings in 8 patients of chronic urticaria who were treated with 15 mg / week of methotrexate, 7 patients showed response to the treatment and 5 patients were in complete remission after taking treatment for mean duration of 3 months[8]. Godse K reported 4 cases of chronic idiopathic urticaria with positive ASST, not responding to antihistamines, were treated with methotrexate 10mg/ week for 2 months responded very well. After methotrexate therapy, urticaria was controllable with only antihistamines in 3 out of 4 patients[9.] In our study, side effects were seen in 9 (15%) out 60 patients and were minimal in the form of nausea and gastritis and there was no dropout of patients due to side effects.

CONCLUSION

Methotrexate can be considered as an effective and safe drug in the treatment of chronic idiopathic urticaria not responding to conventional therapies.

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