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RESEARCH ARTICLE **OPEN ACCESS**

A Retrospective Analysis of Cases of Chronic Spontaneous Urticaria on Treatment with Oral Tofacitinib

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Abstract:

Background: The term chronic spontaneous urticaria (CSU) can be defined as urticaria lasting for more than 6 weeks with no established aetiology. Many newer molecules are being tried for managing the CSU cases not responding to conventional treatment as higher doses of antihistamines, oral steroids, oral methotrexate, oral cyclosporine, omalizumab, *etc*. One such oral agent is tofacitinib. Tofacitinib is known to inhibit the JAK -STAT pathway hence the release of many inflammatory cytokines and so target the pathophysiology of CSU and control symptoms of urticaria. Through this study, we have tried to bring out the efficacy and safety profile of this agent in resolving urticarial symptoms.

Methods: All cases of CSU who had not responded to higher recommended doses of anti-histamine (as per EACI guidelines) and on one or the other immunosuppressive agents were included in the study and based on baseline investigations and patients' response to initial doses of tofacitinib and patient's consent six patients were withdrawn from the study.

Results: Out of 15 patients of CSU included for final evaluation, 10 patients were completely cured of CSU at 6 months and 3 patients responded partially.

Conclusion: Tofacitinib is an innovative molecule for treating antihistamine non-responding cases of chronic spontaneous urticaria.

Keywords: Chronic spontaneous urticaria, Oral tofacitinib, Oral antihistamines, Immunosuppressives, JAK inhibitors, Tofacitinib.

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1. INTRODUCTION

Chronic spontaneous urticaria [CSU] has long been difficult to manage skin conditions. While some cases respond to conventional treatments with antihistamines, many require immunosuppressive medicines. The immunosuppressive medicines used in CSU include cyclosporine as shown in a study by Kanokvalai Kulthanan, Pichanee Chaweekulrat, Chulaluk Komoltri, *et al*. 2018, and methotrexate used for CSU by Sandhu J, Kumar A and Gupta SK. 2022 in their study [1, 2]. The recombinant humanized anti-IgE monoclonal antibody has also been used in a few cases [3]. One recent trial on a new molecule, Bruton Kinase Inhibitor [remibrutinib] in CSU has been conducted by Maurer *et al*. and many similar trials are underway [Maurer *et al*., 2022] [4]. Moreover, steroids are no exception. In different individuals, CSU responds differently to different immunosuppressives. No

options remain when a patient continues to develop urticaria despite escalating doses of antihistamines and even immunosuppressives such as cyclosporin and methotrexate and is not ready for a costly drug: omalizumab. One of the most discussed small- molecules recently tested in such non-responsive CSU cases is a Janus Kinase [JAK] inhibitor, tofacitinib, which inhibits JAK 1/3, inhibiting the signalling of multiple cytokines and hence regulating many inflammatory pathways as evident from a study by Mansouri P, Mozafari N, Chalangari R, and Martits - Chalangari K., 2022, in which magnificent results were seen with the addition of tofacitinib to the ongoing treatment in non- responsive CSU cases [5]. Rhea Singh *et al*. 2020 studied the pathophysiology, efficacy, and safety of JAK inhibitors in atopic dermatitis and concluded that failure to treat this condition with conventional drugs may be an indication for JAK inhibitors [6]. Similarly, off-label use of JAK inhibitors in dermatological diseases including urticaria was studied by BS Dillon Nussbaum *et al*. in 2022 and favoured their use in untreatable CSU cases [7]. One review article "JAK inhibitors in dermatology: The promise of a new drug class." by William Damsky *et al*., 2017 also mentioned its use in various inflammatory conditions of skin including urticaria [8]. Tofacitinib blocks JAK 1/3 hence inhibiting intracellular signalling of multiple key cytokines and hence regulating many such inflammatory processes. One such inflammatory cascade is mast cell activation in CSU patients, which is inhibited by tofacitinib. Adding tofacitinib to antihistamine treatment in urticaria patients not only alleviates intense itching but also helps reduce antihistamine dose.

Thus, tofacitinib can be considered an alternative for treating CSU unresponsive to antihistamines and reducing the duration of treatment and through this study we have aimed to address dermatologists' efficacy and safety concerns while using tofacitinib in CSU treatment.

2. METHODS

After obtaining ethical clearance from the institute's ethical committee, 21 consecutive adult CSU patients who were prescribed oral tofacitinib were included in the study.

The study design was that of a pilot study.

2.1. Inclusion Criteria

(a) Patients in the age group ≥12 years to ≤50 years.

(b) Individuals presenting with CSU and not responding to antihistamines and other immuno-suppressives (oral steroids, methotrexate weekly and cyclosporine).

(c) Patient ready to give consent.

2.2. Exclusion Criteria

Those patients who were pregnant or lactating or had any other comorbidity such as diabetes, hypertension, cardiovascular disease, or any other autoimmune condition such as systemic lupus erythematosus, vitiligo, psoriasis, Hashimoto disease, were excluded from the study.

Then, after taking patients' history, data of patients who had not responded to other immunosuppressives and were now on oral tofacitinib were analysed. Written informed consent was obtained from each one of them.

The demographic details and previous drugs of all patients are presented in Table **1**.

All had been treated with antihistamines in the past and most had been treated with concomitant immunosuppressants; however, urticaria control was not achieved hence oral tofacitinib 5mg BD was prescribed in all such cases after baseline investigations.

Table 1. Demographic features and details of previous and current treatment.

S No.	Age/Sex	Duration Of Disease	Earlier Immunosuppressive Drug	Dermographism Present /Absent	Dose Of Tofacitinib	Dose Of Antihistamines At 1 Month	Dose At 3 Months	Dose At 6 Months And Off Tofacitinib
1	50/F	10 years	Methotrexate 15 mg weekly	Present	5mg bd	Bilastine 20 mg bd	Bilastine 20 mg od	Bilastine 20 mg once weekly
2	21/M	4 years	Methotrexate 15mg weekly	Present	5 mg bd	Bilastine 20 mg bd	Bilastine 20 mg od	Bilastine 20 mg twice weekly
3	15/F	6 months	Cyclosporine 200 mg daily	Not present	5 mg bd	Bilastine 20 mg bd	Bilastine 20 mg od	On no antihistamines
4	33/M	3 years	Methotrexate weekly	Present	5 mg bd	Bilastine 20 mg bd	Bilastine 20 mg od	Bilastine 20 mg alternate days
5	38/M	2 years	Cyclosporine 200 mg daily	Present	5 mg bd	Bilastine 20 mg tid	Bilastine 20 mg bd	Bilastine 20 mg od
6	22/M	2 years	cyclosporine200 mg daily	Present	5 mg bd	Bilastine 20 mg bd	Bilastine 20 mg od	Bilastine 20 mg alternate days
7	26/F	1 year	Cyclosporine 200 mg with intermittent oral steroids to control exacerbations	Not present	5 mg bd	Bilastine 20 mg bd	Bilastine 20 mg bd and levocetrizine 5 mg od in evening	Bilastine 20 mg od and tofacitinib continued
8	20/M	1 year	Methotrexate 15 mg weekly	Present	5 mg bd	Bilastine 20 mg bd	Bilastine 20 mg od	Bilastine 20 mg twice weekly and off

(Table 1) contd.....

S No.	Age/Sex	Duration Of Disease	Earlier Immunosuppressive Drug	Dermographism Present /Absent	Dose Of Tofacitinib	Dose Of Antihistamines At 1 Month	Dose At 3 Months	Dose At 6 Months And Off Tofacitinib
9	50/F	5 years	Methotrexate 15 mg weekly	Present	5 mg bd	fexofenadine 180 mg od, Byloza20 mg od	Fexofenadine 180 od	Fexofenadine 180 mg once weekly
10	45/F	4 years	Cyclosporine 200 mg daily	Not present	5 mg bd	Fexofenadine 180 mg in morning and levocetrizine 5 mg in evening	Fexofenadine 180 mg od	Fexofenadine twice weekly
11	33/F	10 years	Methotrexate 15 mg weekly	Present	5 mg bd Not responding and high lipid profile, high serum IgE	Bilastine 20 mg bd Ranitidine 150 od	Bilastine 20 mg bd	Bilastine 20 mg alternate days
12	34/F	4 years	Cyclosporine 200 mg daily	Present	5 mg bd	Fexofenadine 180 mg tid	Fexofenadine 20 mg bd	Fexofenadine 120 mg od
13	40/F	3 years	Methotrexate 15mg weekly	Present	5 mg bd	Fexofenadine od morning, levocetrizine5 mg evening	Fexofenadine 180 mg bd	Fexofenadine 180 mg od
14	55/ M	3 years	Methotrexate 15 mg weekly	Present	5 mg bd	Fexofenadine 180 mg bd	Fexofenadine 180 mg bd	Fexofenadine 180 mg weekly
15	35/F	5 years	Methotrexate 15 mg weekly	Present	5 mg bd	Tab Desloratadine montelukast	Desloratidine 10 mg od	Desloratidine10 mg twice weekly

Table 2. UAS 7 and UCT scores.

UAS/UCT	At baseline	At 1 month	At 3 months	At 6 months
1.	35/5	28/12	21/16	0/16
2.	42/0	21/4	14/7	7/12
3.	28/4	21/12	14/14	0/16
4.	42/2	21/8	7/10	0/12
5.	28/3	14/5	7/8	0/12
6.	42/0	28/6	14/10	0/12
7.	35/3	28/7	21/12	0/16
8.	28/3	14/10	7/12	0/16
9.	28/3	7/8	0/12	0/12
10.	35/4	21/6	14/10	0/12
11.	42/0	35/4	14/6	0/14
12	42/0	35/6	21/10	0/12
13.	35/0	21/3	14/6	7/12
14.	28/3	21/7	7/12	0/14
15.	42/0	35/3	14/6	7/13

A thorough family history was taken at the start of patient recruitment and recorded to exclude any underlying chronic infection, any other concomitant treatment for diabetes, pain, fever, antiparasitic drugs, or other factors.

The UAS score and urticaria control test [UCT] were recorded at baseline and 1, 3and 6 months follow-up visits and telephonically at 8 months (Table **2**). Furthermore, serum immunoglobulin E and other routine tests were conducted: hemogram, liver function test renal function test, serum lipid profile, thyroid function test, and Mantoux test. These were advised at baseline and routine tests were repeated at follow-up visits.

The findings of the study were evaluated using two-tailed t-test scores.

3. RESULTS

Each patient was prescribed oral tofacitinib 5mg bd for 3 months and antihistamine tablets, for example, bilastine, fexofenadine, desloratadine, levocetrizine, *etc*. were given concomitantly. After 3 months, tofacitinib 5mg was given once daily and at 6 months tofacitinib was stopped. The antihistamines were continued at initial doses and reduced to once daily for 3 months and then alternate days, then twice and once weekly for 1 month each depending on UAS and UCT mentioned in Table **2**. Ten Patients responded very well with UAS7=0 at 6 months and no recurrence at 8 months. Two patients stopped treatment after relief at 3 months. When their symptoms recurred, patients were restarted on treatment but excluded from the study. Two patients continued to have lesions even after 3months of continuous treatment and were asked to

discontinue treatment and were advised cyclosporine as they were previously given methotrexate 15mg once weekly and antihistamine bilastine 20mg. Among the biochemical parameters, serum Ig E was raised in four cases at the start of the study and serum triglyceride was raised in two cases at the end of the first month, these were shifted to weekly methotrexate 15mg and were not included in this study.

On analysing the UAS score and UCT score at baseline and at 6 months (Table **2**), two- tailed T-test p-value for UAS score was <0.0001 and for UCT, it was also <0.0001, both being significant.

4. DISCUSSION

CSU is one of the most discussed dermatology topics regarding treatment resistance. The treating physician sometimes struggles to decide which treatment to give to control disease activity. Tofacitinib, a JAK inhibitor, has now become a small molecule of interest after apremilast and is being tested in many dermatological diseases, including urticaria and is a new hope for future dermatology.

A review article by Sonthalia and Agarwal (2019) discussed the role of tofacitinib in urticaria as well as vitiligo and alopecia areata [9].

Another literature review by Kostovic *et al*. (2017) included 43 papers and concluded that despite encouraging efficacy in psoriasis, vitiligo, atopic dermatitis and alopecia areata, due to safety concerns, more studies are required for these indications and other conditions [10].

A case report by Mansouri *et al*. (2022) observed a good response in four cases of refractory CSU when tofacitinib was added to antihistamines. Thus, according to the authors, tofacitinib can be a good alternative to cyclosporin or methotrexate for treating CSU cases [4].

An observational study by Nettis et,al. found that omalizumab could significantly reduce UAS7 scores to zero in all patients by week 24. However, since not all patients can afford omalizumab, more options are needed [3].

On the contrary, in the same year, F Atsushi, I Mitsuhiro, and N Chikako had for the first time observed the efficacy of oral ruxolitinib in refractory CSU cases [11].

K Benjamine, T Regina, and Jan C. Simon in a mini-review in 2021 have also discussed the overview of the mechanism of action, previous study results, and potential adverse effects of JAK inhibitors including tofacitinib and concluded that it can very well replace glucocorticoids and other immunosuppressives in future [12].

Recently, Emek Kocaturk, Sarbjit S. Saini, Christine J.Rubeiz and Jonathan A. Bernstein together reviewed the existing and investigational medications for refractory CSU and concluded that although extensive research is still lacking in the use of JAK inhibitors (JAKis) in urticaria, due to its broad anti-inflammatory action *via* JAK-STAT inhibition of multiple cytokines as IL-4, IL-5, IL-13, IL-31, IL-22 and TSLP at a time, tofacitinib and other JAKis can be very useful in treating chronic urticarias of autoimmune nature [13].

Similarly, our study of resistant cases of CSU on tofacitinib will be immensely helpful to dermatologists treating such cases of CSU not responding to conventional immunosuppressive treatment with antihistamines.

The novel finding in this study was that no adverse events were observed with this new drug. Moreover, studies on the use of tofacitinib in CSU are few, so larger randomized clinical trials need to be conducted to substantiate its use in refractory CSU cases.

CONCLUSION

Based on this study, it can be concluded that tofacitinib could be the next-generation immuno-suppressive after cyclosporine, methotrexate, omalizumab and steroids, for all immunological conditions including urticaria.

However, tofacitinib, like many other JAK inhibitors, is not free from side effects like cardiovascular events and malignancy. These adverse events can be prevented by avoiding its use in elderly, immunocompromised patients with comorbidities and in those with major cardiovascular events.

LIMITATIONS OF THIS STUDY

Small sample size.

LIST OF ABBREVIATIONS

JAK STAT	=	Janus Kinase
TSLP	=	Thymic stromal lymphopoietin
bd	=	Administered twice daily
Od	=	Once dailyurticaria control test [UCT] w
UCT	=	Urticaria control test

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Institutional Ethical Committee of the Heritage Institute of Medical Sciences, Varanasi with approval no.HIMS/IEC/035.

HUMAN AND ANIMAL RIGHTS

No animals were used in this research. All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional and/or research committee and with the 1975 Declaration of Helsinki, as revised in 2013.

CONSENT FOR PUBLICATION

Informed consent was obtained from all participants.

STANDARDS OF REPORTING

STROBE guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

The data and supportive information are available

within the article.

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CONFLICT OF INTEREST

The authors declare no conflict of interest financial or otherwise.

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