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Case Series

Oral tofacitinib in refractory chronic spontaneous urticaria

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ABSTRACT

Background: Chronic spontaneous urticaria (CSU) is a skin condition marked by the emergence of wheals on their own that persist for six weeks or more. CSU is quite common, affecting up to 1% of the population, and has a serious detrimental effect on a patient's health and quality of life. Antihistamines (AH) are currently the backbone of treatment for chronic urticaria (CU), however up to 40% of patients do not respond to even large (four-fold) daily dosages of AH. Tofacitinib is a small-molecule that inhibits intracellular signalling of several important cytokines involved in the inflammatory cascade and blocks JAK1/3. While there are reports of tofacitinib's positive effects in patients with mast cell activation disorder, there are none in those with urticaria.

Case Series: The aim of our study is to assess the efficacy of oral tofacitinib in refractory chronic spontaneous urticaria. 5 cases of refractory CSU between the age group of 20 to 40 years were included in our study and they were followed up for 6 months. The patients were started on oral tofacitinib 5mg twice a day. On every weekly follow-up, we used clinical assessment, urticaria activity score and urticaria control test to evaluate the treatment response

Conclusion: The usage of oral tofacitinib significantly improves the clinical picture in refractory CSU. Although more research is required to determine Tofacitinib's effectiveness in CSU, our study raises the possibility that it could represent a novel therapeutic option for individuals with refractory CSU.

1. Introduction

Hives, or urticaria, are a common skin condition that affects people all over the world. It could present with or without angioedema.[1] Hives occurring daily or nearly daily for six weeks or longer is known as chronic urticaria (CU).

Between 0.5% and 1% of the general population is thought to be affected by CSU,[2] which primarily affects females between the ages of 20 and 40. Less than 1% of children have CU. There is no discernible difference in the prevalence between males and females among children under the age of 15.

CSU symptoms have a detrimental effect on day-to-day activities, work productivity, sleep quality, and can lower overall health-related quality of life.[3] Given the nature of the condition, CU can be difficult to treat. Although there are many options, many patients do not find the treatment satisfactory. There are resources available to assist practicing physicians in managing this difficult condition, including consensus statements, international updates, guidelines, and consensus statements for the diagnosis and treatment of urticaria from various countries.

First-line Treatment: Start with Second-generation H1-antihistamines, if needed increase the dosage up to 4-fold; Second-line: Add on to non-sedating antihistamines + Omalizumab 300mg every 4 weeks, If needed increase dose or shorten interval; Third-line: Add Cyclosporine; Short

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course (maximum 10 days) systemic corticosteroids may be used at all times if exacerbations demand it[4] 25% of CSU patients, according to a retrospective study, did not respond favourably to even higher doses of non-sedating antihistamines[5,6]

With regard to the molecular biology of diseased cells, the JAK-STAT pathway and its signal transduction in cell proliferation, differentiation, migration, and apoptosis appear to be of paramount importance, especially in light of the recent development of new therapeutic inhibitors to manage inflammation. The persistent activation of the JAKSTAT signalling pathway is closely associated with many inflammatory and autoimmune diseases.[7]

Recent research in CSU has suggested that there are significant interactions between the Janus kinase-signal transducer and activator of transcription (JAK-STAT) signalling and the interferon (IFN)-, interleukin (IL)-2, and IL-21 networks. Cytokines, such as ILs and IFNs, transmit signals from the cell membrane to the nucleus via the JAK-STAT pathway.[8,9]

Tofacitinib, a powerful small-molecule inhibitor of JAK1/3, has been given Food and Drug Administration approval for the treatment of moderate to severe rheumatoid arthritis (RA), psoriatic arthritis (PA), ulcerative colitis (UC), and polyarticular course juvenile idiopathic arthritis. Along with inhibiting JAK1/3, tofacitinib also suppresses the intracellular signalling of several significant cytokines involved in the inflammatory cascade. It inhibits il14 cell-related inflammatory processes.

2. Case Series

Aim of Our Study is to assess the efficacy of Oral Tofacitinib in Refractory CSU. 5 cases between the age group 20-40 years who were resistant to Antihistamines, steroids were chosen for this study. The duration of our study was taken as 6 months, and patients were followed up twice in a month and assessed at every visit. The cases were studied at a Tertiary care hospital.

Pre-treatment Assessment - Patients were investigated before starting the treatment. The following investigations were done -CBC, LFT, Lipid Profile, RFT, IGRA – to r/o latent TB, Chest X Ray, HIV, HbsAg, HCV, Blood Sugar. After the reports, patient was started on Tablet tofacitinib 5mg twice a day and were followed up monthly. Before starting treatment - patients were assessed through Urticaria Activity Score,[10] Complete blood counts, Lipid profile and Liver function test repeated every 2 months No major side effects were noted.

2.1. Case 1

The first case involved a 34-year-old female with a 1-year CSU history. The patient experienced recurrent wheals and angioedema attacks. Throughout a course of systemic steroids, cetirizine, bilastine, doxepin, and fexofenadine, the patient did not respond for six months. Even after quadrupling the antihistamine dose, the symptoms did not get any better. Due to low effectiveness of previous treatment options, the patient was started on oral tofacitinib 5 mg twice daily. Within a few weeks, the urticaria activity score improved. There was a complete remission of the illness with no flare-ups following a month of treatment. The patient was completely symptom-free and did not experience any wheals during the six-month follow-up.

2.2. Case 2

The second patient was a female patient, age 23, with a two-year history of CSU. The patient was experiencing severe pruritus and almost daily wheals. Systemic steroids, Montelukast, levocetirizine, fexofenadine, bilastine, and hydroxyzine were administered to the patient. After a few months of therapy, the patient was still not showing signs of improvement, so we began tofacitinib treatment for her. She initially received 5 mg twice daily. She responded significantly to this treatment after beginning it, and the frequency of her symptoms decreased. Although the patient's condition wasn't completely under control, there was a noticeable improvement from earlier therapies. There was no itching, but there were sporadic wheals every week as opposed to daily wheals. Patient was lost in follow-up for a few weeks, then came back to us and the dosage of Tofacitinib was increased 10mg twice a day which showed complete remission of symptoms within few weeks.

2.3. Case 3

A 28-year-old female with a year of CSU history was the third case. Levocetirizine 10 mg was given to the patient initially at night, followed by 20 mg of bilastine in the morning. As a result of her lack of improvement, we increased the dosage of bilastine to 40 mg and substituted bilastine 20 mg for levocetirizine in the afternoon and at night. The patient did not exhibit any improvement even after the dose was increased. Due to her body's failure to respond to antihistamines, she was also given a course of oral steroids. Even then, the patients' daily quality of life was significantly reduced and the urticaria activity score did not improve. After performing a workup on the patient, tofacitinib 5 mg twice daily was eventually prescribed to her. Patient had significant improvement within a few weeks and complete remission of symptoms by 5^{th} month of treatment.

Table 1:

Patient	Sex/Ag e	Disease Duration	Previous Therapies	Durationof RX with Tofacitinib	Current Status
1	F/34	1 year	AHs, Cs	6 months	Complete control
2	F/23	2 year	AHS, monteleukast	3 months	Significant but not complete
3	F/28	1 year	AHs, Cs	5 months	Complete control
4	M/36	4 year	AHs, Cs	6 months	Complete control
5	M/30	2 year	AHs, Cs	5 months	Complete control

2.4. Case 4

The fourth patient was a 36-year-old man who had chronic urticaria and recurrent angioedema for four years. Patient was experiencing severe pruritus and almost daily urticarial wheals. The score for urticaria activity was 40. The patient experienced an episode of anaphylaxis; he was treated for it by being admitted and given pheniramine and hydrocortisone intravenously. Anaphylaxis was resolved, but the wheals persisted. Although the patient received a short course of oral steroid and an antihistaminic, the wheals persisted even after the pruritus subsided. Tofacitinib 5mg twice a day was started on the patient. Within two months of starting treatment, the patient had no more wheal episodes. For six months, he was kept in the same line of supervision, and total control was seen.

2.5. Case 5

This patient, a 30-year-old man, had a 2-year history of chronic urticaria. Every day, urticarial wheals and excruciating itching occur. The occurrence of wheals was unaffected by any aggravating factors. The patient was given oral corticosteroids in multiple doses in addition to a high oral antihistaminic dosage. From daily to three times per week, wheals occurred less frequently. Pruritus, however, showed no signs of improvement. The severity of the itching interfered with the patient's ability to sleep. We started the patient on Tablet Tofacitinib 5mg twice a day dosing. At first, the patient developed wheals every two to three days, but the itching subsided. Within 5 months of regular intake of Tofacitinib, patient had complete remission of symptoms. The quality of sleep became better since there was resolution of pruritus. The urticaria activity score reduced to zero. Table 1

3. Results

After 6 months of follow up, we noticed complete remission in 4 cases, however 1 patient only showed partial improvement. The clinical situation in refractory CSU was significantly improved by the use of oral Tofacitinib. To ascertain its efficacy in CSU, more research is necessary. Our research suggests that it might represent a cutting-edge therapeutic choice for people with refractory CSU. Tofacitinib is available as generic version in India, It is economical than Cyclosporine/Omalizumab, has a better safety profile. It is devoid of end organ toxicity. It has established efficacy in other auto immune disorders. It has the ability to inhibit signalling from multiple cytokines

Limitations of Cyclosporine-It has a poor safety profile. Renal impairment (which may be reversible upon quitting treatment) and hypertension are the main side effects associated with Cyclosporine. Therefore, throughout the course of treatment, constant monitoring of blood pressure and Blood urea Nitrogen, serum creatinine is necessary. Higher cost of the medication also limits its use.

Limitations of Omalizumab- It has to be given in a hospital setting, Higher cost, can lead to Injection site reactions, it is Available only as biosimilar in developing countries.

4. Discussion

CSU is characterised by wheals and itching that appear daily or nearly daily and last for at least six weeks. It has been determined that the underlying mechanism for this allergic reaction is the activation of cutaneous mast cells. It is known that inflammation plays a role in CSU and that it is brought on by a complicated interplay between pro-inflammatory mediators, cytokines, and adhesion molecules that control progressions of cellular infiltration and vasoactivity.[11,12]

Cytokines released in the body in cases of Chronic spontaneous urticaria further promote inflammation and immune response in the affected skin. These cytokines are responsible for recruitment of other immune cells to the site of inflammation. The persistence of urticarial lesions can also be attributed to the elevated levels of certain pro-inflammatory cytokines in the body.

Many cytokines and growth factors share the JAK/STAT signalling pathway.

The development of CSU is accelerated by the upregulation of IL-9/10, whereas the formation of CSU can be efficiently suppressed by the suppression of the JAK/STAT signalling pathway.[13]

Antitumor immunity, autoimmune inflammation, and human and murine atopic disorders are all significantly impacted by IL-9.A pleiotropic cytokine, IL-9 affects

various cell types directly or indirectly. For instance, it increases the amount of IgE that B cells produce, and it is a strong growth factor that encourages mast cell proliferation and differentiation. [14]

Another inflammatory cytokine that is mostly generated by Treg cells is IL-10. According to certain theories, IL-10 levels are raised in CSU patients in attempt to reduce inflammation.

By acting through the transmembrane receptor gp130, IL-6 and other cytokines can activate the JAK/STAT signalling system, specifically JAK2/STAT3, and once activated, STAT3 positively regulates several proinflammatory gene profiles. Increased IL-6/IL-6 sR complex formation in the bloodstream is caused by heightened IL-6 sR, which also increases the expression of proinflammatory mediators. This increased expression of proinflammatory mediators can stimulate a wide variety of cells.

In comparison to healthy volunteers, the plasma concentration of IL-6 sR was considerably greater in CSU patients. The higher IL-6 sR and IL-6 concentrations in CSU show that IL-6 acting through IL-6 sR boosts the trans-signalling capability as a component of the inflammatory response, which may in turn increase the disease activity. According to certain research, IL-6 trans-signalling plays a crucial role in the upkeep of many clinical disorders by fostering chronic inflammation. [15]

JAK inhibitors can indirectly block other STAT-dependent cytokines, such as TNF-, IL-1, and IL-17, even though these cytokines do not rely on the JAK/STAT pathway.

These are chosen over biologics due to their propensity to suppress various cytokine signals and the ease with which they can be administered (orally or topically). JAK inhibitors cause the intracytoplasmic transcription factors STATs to become active, which controls the inflammatory process. STATs become dimers after activation and go into the nucleus where they regulate the expression of several genes.

These fresh understandings of the CSU aetiology can help in the future development of more potent treatments for this allergic condition.

5. Conclusion

In this study, we found that Tofacitinib administered as 5mg twice daily dosage significantly reduced symptoms in patients with chronic spontaneous urticaria who remained symptomatic despite the use of approved doses of H1-antihistamines. The number of patients who were treated is insufficient to make any firm safety inferences. Prior to defining Tofacitinib's precise role in the management of chronic spontaneous urticaria, more research is required.

6. Patient Consent Statement

The patients in this study have provided written informed consent for the publication of their case information.

7. Conflict of Interest

The authors declare no conflicts of interest.

8. Source of Funding

None.

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