COMPARISON OF THE EFFICACY OF ORAL LEVOCETIRIZINE, BILASTINE AND FEXOFENADINE IN CHRONIC SPONTANEOUS URTICARIA: AN OPEN-LABELLED RANDOMISED CONTROLLED TRIAL

Thesis

Submitted to

All India Institute of Medical Sciences, Jodhpur

In partial fulfillment of the requirement for the degree of

DOCTOR OF MEDICINE (MD)

(DERMATOLOGY, VENEREOLOGY AND LEPROLOGY)

JULY, 2020
AIIMS, JODHPUR

DR. SHILPI TYAGI

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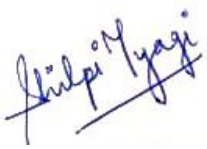
DECLARATION

I hereby declare that the work reported in the thesis entitled "Comparison of the efficacy of oral Levocetirizine, Bilastine and Fexofenadine in Chronic Spontaneous Urticaria: An Open-labelled Randomised Controlled Trial" embodies the result of original work carried out by the undersigned in the Department of Dermatology, Venereology and Leprology, All India Institute of Medical Sciences, Jodhpur.

I further state that no part of this thesis has been submitted either in part or in full for any other degree of All India Institute of Medical Sciences, Jodhpur or any other institution.



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CERTIFICATE

This is to certify that the thesis titled "**Comparison of the efficacy of oral Levocetirizine, Bilastine and Fexofenadine in Chronic Spontaneous Urticaria: An Open-labelled Randomised Controlled Trial**" is the bonafide work of **Dr. Shilpi Tyagi**, in the Department of Dermatology, Venereology and Leprology, All India Institute of Medical Sciences, Jodhpur.

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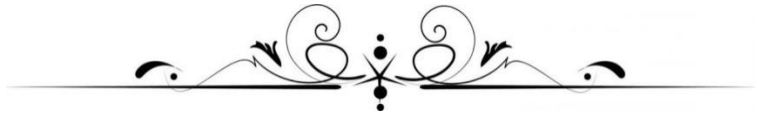
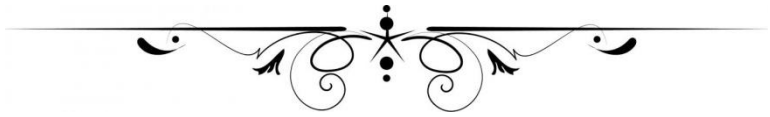


DEDICATED TO MY FAMILY,

TEACHERS AND PATIENTS.



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"Let me not pray to be sheltered from dangers, but be fearless in facing them.
Let me not beg for the stilling of my pain, but the heart to conquer it."

-Rabindranath Tagore.

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Dr Shilpi Tyagi

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ABBREVIATIONS

CU	Chronic urticaria
CSU	Chronic spontaneous urticaria
IgE	Immnuoglobulin E
IgG	Immnuoglobulin G
PAF	Platelet activating factor
sgAH	Second- generation H1 antihistamines
H1R	Histamine 1 receptor
DLQI	Dermatology life quality index
UAS7	Urticaria activity score 7
CU-Q2oL	Chronic urticaria quality of life questionnaire
UCT	Urticaria control test
CIU	Chronic inducible urticaria
TNF	Tumour necrosis factor
ASST	Autologous serum skin test
BAT	Basophil activation test
BHRA	Basophil histamine release assay
PTPN22	Protein tyrosine phosphatase 22
CRTH2	Chemoattractant receptor homologous molecule 2
ICAM-1	Intercellular adhesion molecule-1
DNAM-1	DNAX accessory molecule 1
MCP-1	Monocyte chemotactic and stimulating factor
TPO	Thyroid peroxidase
VEGF	Vascular endothelial growth factor
FXa	Factor Xa
PAR1	Protease-activated receptor 1
VIP	Vasoactive intestinal peptide

HPA	Hypothalamus-pituitary-adrenal
DHEAS	Dehydroepiandrosterone-sulphate
CRH	Corticotrophin releasing hormone
HC	Healthy controls
ASST	Autologous serum skin test
sR	Soluble receptor
LCN2	Lipocalin-2
ES	Endostatin)
TSP-1	Thrombospondin-1
MMP-9	Matrix metalloproteases 9
ICAM-1	Intercellular adhesion molecule-1
VCAM-1	Vascular cell adhesion molecule-1
sVE-cadherin	Endothelial cadherin
QoL	Quality of life
PRO	Patient-reported outcome
HRQoL	Health-related quality of life
UV	Urticarial vasculitis
CRP	C-reactive protein
ESR	Erythrocyte sedimentation rate
CBC	Complete blood count
H4R	Histamine 4 receptor
NF-kB	Nuclear factor kappa-B
NO	Nitric oxide
mAb	Monoclonal antibody
H1-AH	H1 antihistamine
LTRA	Leukotriene receptor antagonist
IQR	Interquartile range

SUMMARY

Background: Second generation antihistamines are recommended as first line drugs in treatment of chronic spontaneous urticaria, however, their relative efficacy is not well established. Literature comparing the efficacy of various antihistamines is limited. Moreover, basophil count has been proposed as marker of disease activity and treatment response. Studies analysing basophil counts with respect to treatment with antihistamines are lacking. Hence, we wanted to compare the efficacy of bilastine with more commonly used antihistamines like levocetirizine and fexofenadine as well as to compare the effect of treatment on basophil counts.

Objectives: To compare the efficacy of oral Levocetirizine, Bilastine, and Fexofenadine in the treatment of Chronic Spontaneous Urticaria.

Materials and Methods: It was an open labelled randomised interventional study. A total of 95 patients were recruited in the study of which 11 patients were lost to follow up. Relevant history was taken and clinical examination was performed. At baseline, recording of UAS7, CU-Q2oL, DLQI scores and assessment of basophil counts was done. Patients were randomly allocated into 3 groups and received either oral levocetirizine (5 mg once daily), bilastine (20mg once daily) or fexofenadine (180 mg once daily). Follow up was done at 2 weekly intervals for 6 weeks and patients were assessed for response to treatment and treatment related side effects. Patients reporting inadequate control at follow-up were subjected to dose escalation to a maximum of four-fold. At the end of 6 weeks, UAS7, CU-Q2oL, DLQI scores and assessment of basophil count was repeated which were analysed statistically with their baseline values. Statistical analysis was done using SPSS software v.26 and $p - value < 0.05$ was considered significant.

Results: All the drugs (levocetirizine, bilastine and fexofenadine) caused a significant decline in UAS7 score, which was comparable across all the groups. The dose escalation required for control of urticaria in patients with inadequate response was comparable between three groups. None of the groups documented a significant change in basophil count at the end of the study. Quality of life scores like CU-Q2oL and DLQI showed significant decline from baseline and resulted in comparable scores at the end of 6 weeks in all the groups. All the treatment groups were similar in their side effect profile

Conclusion: The three drugs (levocetirizine, bilastine and fexofenadine) are equally efficacious in the treatment of CSU. Up-dosing of antihistamines in patients with inadequate response can augment the control of symptoms in these patients. These drugs have mild and comparable side effects. Role of basophil counts as marker of treatment response could not be concluded in our study but we cannot rule out its utility in the future.

INTRODUCTION

INTRODUCTION

Chronic urticaria (CU) is a common inflammatory disorder of skin that lasts for more than 6 weeks and is characterised by appearance of wheals, angioedema or both. It is classified as spontaneous if the wheals appears unprovoked and induced if an inciting stimulus is known.[1] Chronic spontaneous urticaria (CSU), previously known as chronic idiopathic urticaria ,is the most common form of chronic urticaria accounting for 21-83% of CU.[2]

It affects all ethnicities and has a point prevalence of 0.02-2.7%. [1] It generally lasts for 2 to 5 years in majority of patients. However, approximately 20% patients experience urticaria even beyond 5 years.[3] It occurs across all age groups with greater incidence in adults. Women are more commonly affected by CSU. It may be familial in approximately 25% of patients. Association of CSU with other autoimmune conditions such as autoimmune thyroid disorders, connective tissue disorders and type I diabetes mellitus have been proposed.[1]

Exact etiology of CSU is unknown. However, mast cell activation is central to its pathogenesis.[4] A multitude of triggers, both immunological as well as non-immunological lead to crosslinking of FcεRI receptors via allergen specific Immunoglobulin E (IgE). This activates several mast cell membrane proteins finally resulting into its degranulation. Non-immune mechanisms include dysregulation of intracellular signalling with functional or trafficking defects in mast cells and basophils.[5] Two autoimmune mechanisms have been postulated for mast cell activation. First involves crosslinking of FcεRI receptors on mast cells by Immunoglobulin G (IgG) autoantibodies against IgE or FcεRI. Second mechanism includes presence of IgE antibodies directed against autoallergens.[4] Release of histamine and other mediators like platelet activating factor (PAF), tryptase, leukotrienes and cytokines causes pruritus and wheal formation by sensory nerve stimulation, vasodilation, plasma cell extravasation and recruitment of inflammatory cells.[5]

Basophils also play an important role in the pathogenesis of CSU. They share structural homology with mast cells in terms of granules and FcεRI receptors which releases histamine. Takimoto-Ito *et al.* hypothesized that migration of activated basophils to skin in CSU leads to peripheral basopenia. Decreased peripheral basophil counts have been related to more symptomatic CSU. Increased cell surface expression of CD203c, an activation marker of basophil, is observed in treated patients of CSU. Role of coagulation cascade and complement system has also been implicated in the pathogenesis of CSU .[6]

CSU is primarily a clinical diagnosis. Mimickers of CSU like urticarial vasculitis, cutaneous mastocytosis, autoinflammatory disorders, etc. needs to be excluded. Basic investigations

such as differential cell count, erythrocyte sedimentation rate, C-reactive protein is useful in some patients.[7]

Current international EAACI/GA²LEN/EuroGuiDerm/APAAACI guidelines for management of urticaria proposed a stepwise approach. Treatment is started with standard dose of second-generation H1 antihistamines (sgAH). While on treatment, patients should be assessed regularly for clinical response. In case of partial or no response, up-dosing of sgAH is permitted for a maximum of four-fold, after 2-4 weeks or earlier. Numerous studies have supported the use of four-fold dosage of antihistamines like cetirizine, levocetirizine, desloratadine, fexofenadine, rupatadine, ebastine and bilastine in urticaria .[7-11] On achieving clinical control, a step-down approach is suggested for decreasing the dose of antihistamine. In case of insufficient symptom control other modalities including anti IgE monoclonal antibody like omalizumab and immunomodulators like cyclosporine can be offered. Other drugs used include leukotriene receptor antagonists, H2 antihistamines, doxepin, dapsone, sulfasalazine, methotrexate and mycophenolate mofetil. Besides symptomatic treatment with antihistamines, other comorbidities and disease modifying factors needs to be addressed adequately[7]

It is pertinent to emphasize that H1 antihistamines reduce pruritus by acting on C type fibres, erythema by attenuating axon reflex and wheal formation by acting on endothelium of post capillary venules.[12]

CSU has a significant impact on the quality of life of patients because of severe pruritus that disturbs sleep and routine activities. In addition, the disease generally has an unpredictable course and in cases where angioedema coexists, there can be an element of disfigurement. Although this disfigurement is temporary in nature. Therefore, due importance should be given to patient reported outcomes on quality of life. These include dermatology life quality index (DLQI), disease activity scores like urticaria activity score 7(UAS7), chronic urticaria quality of life questionnaire (CU-Q2oL) , weekly activity interference score, and score for disease control, such as urticaria control test (UCT). [13]

As stated earlier, the mainstay of management of CSU are sgAHs. There have been constant efforts to find newer agents with better efficacy and lesser side effects. In India, bilastine was approved for the symptomatic treatment of allergic rhinoconjunctivitis and urticaria in adults in 2019. There is relatively less literature comparing the efficacy of various second generations H1 antihistamines Moreover, the role of basophils as markers of disease activity is emerging. Therefore, through this study we aim to compare the efficacy and side effect profile of three oral second-generation H1 antihistamines namely levocetirizine, bilastine and

fexofenadine in patients of CSU. We also intend to compare the effect of treatment on basophil count and impact thereof on quality of life.

AIM & OBJECTIVES

AIM & OBJECTIVES

AIM OF THE STUDY

To compare the efficacy of oral Levocetirizine , Bilastine, and Fexofenadine in the treatment of Chronic Spontaneous Urticaria.

OBJECTIVES

PRIMARY OBJECTIVE:

1. To compare the clinical improvement between Levocetirizine, Bilastine, and Fexofenadine treatment groups in the treatment of Chronic Spontaneous Urticaria using UAS7.

SECONDARY OBJECTIVES:

1. To compare the pre and post-treatment basophil count between the three treatment groups.
2. To assess the effect of treatment on CU-Q2oL and DLQI.
3. To compare the side-effects between different treatment groups.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Urticaria is a common inflammatory skin condition affecting upto 20% of the world population.[1]

HISTORY

One of the earliest descriptions of urticaria is noted in Chinese literature, *Huangdi Neijing*, which refers urticaria as *Feng Yin Zheng* which means 'wind type concealed rash'. This expression is similar to the term used currently in traditional Chinese medicine, *Feng Sao Yin Zhen* meaning 'wind itch concealed rash' as wind was considered one of the causative factors of urticaria.[14]

Hippocrates , known as the 'Father of Modern Medicine' used the term '*knidosis*' to refer to the raised itchy lesions brought on by nettles plant (knido in Greek). He was the first to mention gastrointestinal disorders as a possible cause of urticaria. Different ancient literature have advocated various terminologies to describe urticaria, e.g., ancient Latin medical literature used the term *'uredo'* which means to burn; and old Persian texts as *'essera'* implying elevation. The German used the term '*Leusschieppen*' which was introduced by Paracelsus. In the 18th century William Cullen first used the term " urticaria" which apparently was derived from *Urtica urens* (annual nettle). The first description of angioedema came around 16th century by Marcello Donati , who noted that these appeared after food intake. By mid 1800s, urticaria and angioedema were acknowledged to be similar in nature. [14]

Food intolerance or poisoning were considered as the cause of urticaria since ancient times.

Other than food, many other conditions and factors have been considered causal for urticaria.

The spectrum of theories on etiology of urticaria ranges across idiosyncratic theory, humoral theory, toxin theory, nervous theory, microthrombosis theory, menstrual theory, angioneurotic theory, theory of inflammation and meteorological theory.[14]

EPIDEMIOLOGY

Urticaria is an under-diagnosed condition with a lifetime prevalence of 15 to 20% but this data is likely under-represented.[15]

Acute urticaria is more common in children and carries a lifetime prevalence of 6-19%.[1]

Chronic urticaria occurs all across the globe with a lifetime prevalence of 4.4% and point prevalence of 0.7%. It affects all ethnicities and various regions show different point

prevalence, e.g. 0.7% in North America,0.5% in Europe, 1.4% in Latin America and around 1.5% for Asian Countries. Last decade witnessed a 2 to 10 fold rise in the prevalence of CU. Individuals across all age groups are affected. However, urticaria primarily affects young to middle aged adults with peak incidence seen around 20 to 40 years. In adults, chronic urticaria is more commonly observed in females. This gender predisposition is not seen in children or the elderly. [16]

The prevalence of chronic inducible urticaria is unknown. However, 7 to 30% adult patients of CSU concomitantly have chronic inducible urticaria (CIU). Similarly, 14% cases of CIU also suffer from CSU. The median age of onset for CIU is about 40 years.[16]

CLASSIFICATION OF URTICARIA

Urticaria can be temporally classified into two types- acute and chronic, chronic urticaria implying disease lasting for more than 6 weeks. Based on eliciting factors, it can also be classified into inducible and spontaneous subtypes. Development of wheals, angioedema or both in response to definite and subtype-specific triggers is characteristic of inducible urticaria.[7] In spontaneous urticaria, there are no definite triggers and signs and symptoms appear unprompted. Few patients of spontaneous urticaria exhibit increased disease activity in states of stress , infections and other factors.

RISK FACTORS

High population density, personal and family history of allergic diseases are reported risk factors for acute urticaria. Higher prevalence of acute urticaria is noted in lower socioeconomic groups. Whereas chronic urticaria is linked to high socioeconomic status. Genetic factors also contribute to the susceptibility to urticaria. Polymorphism in genes, such as TNFRS11A, TBXA2R and PLA2G4A impart susceptibility to acute urticaria or angioedema on exposure to NSAIDs. While, genetic polymorphism in IFNγ, IL-6, IL-17RA, IL-10, TGFβ, tumour necrosis factor (TNF), PTPN22, IL-1, IL-2 and HLA class I and II alleles predisposes to chronic urticaria.[1]

PATHOGENESIS

The causation of chronic spontaneous urticaria is multifactorial. It involves autoimmunity, intracellular signalling in mast cells and basophils and coagulation cascade.[17] Interactions between inflammatory cells and nerves also comes into play.[1]

1. THE AUTOIMMUNE THEORY

The autoimmune theory is a widely accepted hypothesis in the pathogenesis of CSU. It provides a lucid explanation for abnormal activation of mast cells and basophils in these patients.[18] Autologous serum skin test (ASST), basophil activation test (BAT), and basophil histamine release assay (BHRA), etc. can be used for diagnosis of autoimmune CSU. Approximately 45-50% CSU patients harbour IgG autoantibodies against IgE or its high-affinity receptor (FcεRI).[17] Out of the two antibodies, anti- FcεRI antibodies are generally more prevalent.[18]

Dermal mast cells and basophils both harbour the FcεRI-α receptor on their surface. Autoantibodies against this receptor cause persistent activation and degranulation of both mast cells and basophils without involving IgE. On the other hand, IgG-anti IgE antibodies lead to activation and degranulation of mast cells and basophils by binding to receptor-bound IgE and crosslinking it on the surface of these cells. Presence of autoantibodies does not necessarily translates into a disease phenotype, as is the case with other autoimmune diseases. FcεRI-α autoantibodies have been detected in the sera of patients with different autoimmune skin disorders as well as in healthy individuals, but they have not been proven to significantly increase histamine release. This discrepancy is attributed to the fact that chronic urticaria patients likely have anti- FcεRI-α antibody of the complement-fixing IgG1 and IgG3 subtypes, whereas patients with other inflammatory skin disorders tend to have IgG2 and IgG4 subtypes. Other researchers have demonstrated that in vitro basophil activation and subsequent histamine-releasing activities do not correlate with the existence of anti-FcεRI-α autoantibodies in patients with CSU. The presence of autoantibodies to IgE and FcεR1 in CSU implies the existence of antigen-specific lymphocytes. It is noted that a significant proportion of patients with CSU have FcεR1-specific T lymphocytes, which elicitse a Th1 cytokine response. This subset of patients also show comparable proportions markers of T cell activation and mast cell degranulation. Protein tyrosine phosphatase 22 (PTPN22) is a strong susceptibility gene for a various autoimmune disorders. It encodes a lymphoid specific tyrosine phosphatase, which under normal circumstances acts as an inhibitor of T cell activation. Variations in this gene corroborates with the involvement of T lymphocytes in the pathogenesis of CSU.[18]

The existence of autoantibodies against a backdrop of persistent inflammation is common to all autoimmune diseases. Due to the extreme heterogeneity of these diseases, it is challenging to determine whether the association between chronic urticaria and aforementioned diseases is caused by a shared pathology or is merely the result of detection bias.[18]

2. THE CELLULAR CROSS TALK

Patients of CSU show significant infiltration of eosinophils, neutrophils, basophils, and macrophages in the dermis and deep dermis.

I. Role of Mast cells

It is well recognised that mast cells play a major role in CSU. They are cells of the innate immune system , which are found surrounding the blood vessels and nerves. A variety of extracellular triggers, including antigen-IgE complex, cytokines produced by other inflammatory cells, viruses, bacteria, and microvesicles can cause activation of mast cells. IgE-dependent mast cell degranulation intensifies on exposure to allergens or other environmental conditions i.e. cold, heat, or pressure. In addition to IgE-induced mast cell activation, Mas-related G-protein coupled receptor-X2 (MRGPRX2), which is highly expressed in cutaneous mast cells, has a critical role in CSU. The release of individual granules from mast cells was more regular and rapid after MRGPRX2 activation.

Furthermore, soluble mediators, partly through cell-to-cell interactions and microvesicles, are responsible for the local as well as systemic effects of mast cells. Microvesicles are present in the majority of bodily fluids. They are nanoscale vesicular particles released by different cell types. Both resting and degranulating mast cells can secrete microvesicles, which act as a means of inter-cellular communication. Additionally, recent studies have shown that mast cells can be activated by microvesicles produced by T cells. These studies emphasise the possibility of functional interactions between mast cells and other cells that go beyond cell-to-cell connections or soluble mediators. Histamine, tryptase, chymase, carboxypeptidase, cathepsin G, PAF, leukotrienes, prostaglandins, cytokines, and chemokines are the preformed and de novo mediators released by activated mast cells. These mediators increase vascular permeability, lead to chemotaxis of other inflammatory cells and causes wheal and flare.[17]

Mast cells play a crucial role in the development and dynamics of adaptive immunity in CSU, which is described as follows :-

(i) The production of TNF-α and other mediators for up-regulating the expression of adhesion molecules on vascular endothelial cells in order to promote the recruitment of T cells.

(ii) Activation of mast cells and basophils by allergen-specific Th2 cells, which in turn drives B cells to produce IgE antibodies.

(iii) The induction or modulation of T-cell activation and polarisation.[17]

II. Role of Basophils

Similar to mast cells, basophils also release histamine and other pro-inflammatory mediators (such as PAF, leukotriene C4, IL-13, IL-25, and CXCL8/IL-8) after activation, which cause vasodilation in lesions of urticaria. Histamine released by these cells acts on basophils to increase their chemotaxis and regulates the IgE-dependent activation via a negative feedback loop.[17]

PGD2 is an endogenous agonist of receptor chemoattractant receptor homologous molecule 2 (CRTH2) which is expressed on the surface of a number of cells, including basophil and mast cells. Release of PGD2 by activated mast cells incites intracellular mobilization of calcium, up-regulation of CD11b and enhanced antigen-mediated histamine release by basophils.[17]

IL-3 is required for growth and development of basophils. It enhances FcεRI expression on basophils and increases their responsiveness to other stimuli. Basophils also influence the mast cells at the site of inflammation by robust production of IL-4, in response to both IgE-dependent and independent stimuli. IL-4 regulates the phenotype, growth, and differentiation of mast cells and enhances expression of FcεRI on their surface. [17]

Stimulation of basophils by anti-IgE, IL-3, or N-formylmethionylleucyl-phenylalanine leads to release of IL-31 that induces the releases of IL-4 & IL-13 from basophils. IL-33 is another cytokine that amplifies the allergic response in mast cells and basophils through tumorigenicity 2 receptor. [17]

III. Role of Eosinophils

Mast cells and eosinophils interact through an intricate web of paracrine and membrane interactions. The physical interaction between these cells, mediated by CD48-2B4, stimulates IgE-activated mast cells and increases release of basal mast cell mediators. There is an increase in intercellular adhesion molecule-1 (ICAM-1) on eosinophils which promotes their adhesions with mast cells. ICAM-1 also prolongs the survival of eosinophils. Co-stimulatory signals from eosinophils lower the threshold of IgE response of mast cells. Interaction between DNAX accessory molecule 1 (DNAM-1/CD226) on mast cell and Nectin-2 (CD112) of eosinophils enhances mast cell activation.[17]

Recruitment of eosinophils to diseased skin occurs in response to release of eotaxin, PDG2 and histamine from mast cells. PDG2 promotes release of eosinophil cationic protein and activation of eosinophils. The survival of eosinophils, expansion and maturation of their progenitor cells and innate inflammatory process producing wheals are mediated by IL-5. Eosinophil derived tissue factors activate the extrinsic coagulation cascade and complement protein C5a.[17]

IV. Role of T cells

T lymphocytes and mast cells interact through direct contact, release of microvesicles and inflammatory mediators. Direct contact between these cells mediates activation of T- cells by co-stimulatory molecules present over the surface of mast cells. Pro-inflammatory mediators secreted by mast cells drive leukocyte migration and extracellular matrix degradation. Histamine shifts the balance towards production of Th2 cytokines and inhibition of Th1 cytokines. Microvesicles, released by T-cells, activate mast cells in a contact-independent manner to release inflammatory mediators.[17]

V. Role of other cells

Activated monocytes release monocyte chemotactic and stimulating factor (MCP-1) which mediates release of histamine and other inflammatory mediators from mast cells and basophils. Tissue factor released by monocytes increases vascular permeability and activates exogenous coagulation pathways that further activates mast cells and basophils.[17]

IL-6 from macrophages increases proliferation, maturation and reactivity of mast cells. B lymphocytes produce IgE/IgG antibodies to autoantigens like thyroid peroxidase (TPO) and IL-4.[17]

3. COAGULATION CASCADE AND COMPLEMENT PATHWAY

Histamine, vascular endothelial growth factor (VEGF), lipopolysaccharides , TNF-α, IL-6, IL-33 and IL-1β are inducers of tissue factor. Eosinophils and endothelial cells of dermal microvasculature show robust expression of tissue factor in response to these mediators. Activation of extrinsic coagulation pathway by tissue factor leads to production of activated coagulation factors like factor Xa (FXa) and FIIa (thrombin). These factors in conjunction with histamine, VEGF, bradykinin, PAF and other mediators act through protease-activated receptor 1 (PAR1) to form gaps between the endothelial cells of dermal vasculature. Following this, plasma containing anti-IgE or anti-FcεRI antibodies, and/or autoantigens for specific IgE bound to mast cells leaks from the dermal vessels. This dermal fluid and mast cell activation gives rise to wheal and flare formation. Mast cell degranulation also occurs by action of thrombin and FXa on PAR1 and PAR2, respectively.[1]

Complement components i.e. C3a and C5a can also activate mast cells and basophils. They are produced from C5 and C3 respectively, by the action of FXa and FIIa.[1]

4. ROLE OF THE NERVOUS SYSTEM

Cutaneous mast cells release several mediators including histamine, cytokines like IL-31 and growth factors that bind with receptors on sensory nerve endings, stimulating the itch sensation. Reciprocally, nerve endings release neuropeptides such as substance P and vasoactive intestinal peptide (VIP) etc. that activate mast cells and promote inflammation.[19] Stressful events can trigger the exacerbation of urticaria. The link between the central nervous system and the cutaneous immune system is mediated through C-fibre sensory nerves. The nerve endings release numerous neuropeptides including substance-P and calcitonin gene related peotide (CGRP). Neuropeptides directly stimulate mast cells through various receptors. They also modulate dendritic cell function to polarize Th cell function along specific pathways.[20] The connection between psychiatric stress and the skin may also be mediated through the neuroendocrine axis – the hypothalamus-pituitary-adrenal (HPA) axis which increases adrenal glucocorticoid synthesis and suppresses the production of sex steroids like dehydroepiandrosterone-sulphate (DHEAS). Chronic stress fatigues the HPA axis the leading to hypocortisolism. This leads to increased Corticotrophin releasing hormone (CRH) release by the hypothalamus as well as by epidermal and hair follicle keratinocytes. The excess CRH directly stimulates mast cells through its receptors contributing to urticaria-associated inflammation.[21]

CLINICAL FEATURES

Urticaria presents with wheals and/or angioedema. Wheals are well-circumscribed superficial swellings of varying shapes and sizes, surrounded mostly by a zone of erythema. Wheals are transient in nature that usually resolve within 30 minutes to 24 hours, leaving behind normal appearing skin. They are associated with itching or sometimes burning sensation.[7]

On the other hand, angioedema is a sudden onset deep swelling of lower dermis and subcutaneous tissue or of the mucosa. It can be erythematous or skin-coloured and takes longer i.e. up to 72 hours to resolve. Angioedema may have tingling , burning sensation, tightness or pain instead of itching.[7]

ASSOCIATIONS OF URTICARIA

Few comorbidities, such as autoimmune disorders, psychiatric and atopic disorders occur more frequently in patients of urticraia. The same cannot be applied to malignancies, cardiovascular and gastrointestinal disorders co-existing with chronic urticaria.[5]

Among autoimmune comorbidities, most common ones are autoimmune thyroid disorders and vitiligo, followed by connective tissue disorders like systemic lupus erythematosus (SLE) and rheumatoid arthritis. HIigher levels of anti-thyroid peroxidase (anti-TPO) antibodies, antinuclear antibodies (ANA), antithyroglobulin antibodies, rheumatoid factor, anti-transglutaminase IgA antibodies, and anti-parietal cell antibodies with anti-dsDNA, and anti-cardiolipin antibodies are noted in patients with CSU when compared to healthy controls.[5,18]
Atopic disorders, such as, atopic dermatitis, asthma and rhino-conjunctivitis are more prevalent in antihistamine unresponsive chronic urticaria. CU patient have higher incidence of anxiety, depression and somatoform disorders and emotional stress.[5]

MIMICKERS OF URTICARIA

Wheals and/or angioedema can occurs in diseases other than urticaria. In such situations, history and physical examination, along with laboratory test can aid in making the diagnosis.[1]
Atypical urticarial lesions present with a more symmetrical distribution, infiltration and coexistence with other skin lesions (papules, vesicles and haemorrhages). These lesions last longer than 24 hours and resolve with hypopigmentation/ hyperpigmentation or scaling. Angioedema may also occur sometimes. Presence of systemic symptoms such as fever, malaise, arthralgia along with the above-mentioned features dissuades the diagnosis of urticaria.[22]
Other dermatological diseases like polymorphic light eruption, maculopapular cutaneous mastocytosis, bullous pemphigoid, erythema annulare centrifugum, autoimmune progesterone dermatitis, urticarial dermatitis, maculopapular drug exanthema, and sweet's syndrome can be considered as differential diagnosis of acute urticaria. Intermittent crops of atypical wheals emulating chronic urticaria, occur in urticarial vasculitis, hypereosinophilic syndromes, mast cell activation syndrome and auto inflammatory urticarial syndromes. Similarly, angioedema without wheals can also occur in mast-cell mediated angioedema, bradykinin-mediated angioedema and hereditary angioedema.[22]

BIOMARKER

A biomarker is defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention" by National Institute of Health (NIH) Biomarkers Definitions Working Group.[23] An ideal biomarker should have the following qualities: high sensitivity, high specificity, reproducibility, ease of measurement and validity. [24] CSU shows remarkable

heterogeneity in clinical characteristics, associated conditions and responsiveness to the prescribed medicines. Therefore, a biomarker, which can categorise patients according to their phenotype, immunological mechanisms, severity, prognosis and response to treatment, can be clinically significant. [25]

1. IMMUNOLOGICAL BIOMARKERS

Although causes of mast cell activation in CSU are mostly unclear and unidentified, IgG autoantibodies directed against TPO, IgE, or their high-affinity IgE receptor (FcRI) have been detection in a subgroup of CSU patients. Up to 33% of CSU patient possess IgG anti-TPO antibodies which is associated with a prolonged duration of urticaria. Hence, IgG anti-TPO antibodies can be taken as a probable indicator of disease course.[26]

IL-24 is an autoantigen against which IgE antibodies are detected in a significant proportion of CSU patients as compared to healthy controls (HC). Schmetzer *et al.* found a strong correlation between presence of anti-IL-24 IgE antibodies and reduced basophil count and severity of CSU.[25,26]

A study by Straesser *et al.* showed that lower levels of total IgE seems to correlate with reduced efficacy of omalizumab and with time taken to relapse after stopping treatment.[26,27]

Immune system involvement also extends to the activation of the complement system. Patients of CSU exhibit high levels of C3 and C4 which correlates well with levels of C-reactive protein (CRP). However, this increase has been observed only in 5-10% cases of CSU thereby limiting their use as biomarkers of disease activity. Anaphylotoxins such as C3a and C5a have a role in urticarial inflammation but their utility as biomarker of CSU is yet to be proven.[26.]

As per the recent guidelines of urticaria, autologous serum skin test (ASST) and basophil activation test (BAT) can be used to screen the autoantibodies in CSU.[26]

Autologous serum skin test (ASST)

ASST is an in-vivo clinical assay to detect histamine-releasing activity of basophils. It was first described in 1986 for differentiating autoimmune urticaria from chronic spontaneous urticaria. It has a sensitivity and specificity of 70% and 80% respectively. Diagnosing patients of autoimmune urticaria may be beneficial as these patients may require substantial doses of antihistamines, systemic corticosteroids (during acute exacerbations), and immunomodulatory medications for their treatment.[28.]

Ghosh *et al*. described the procedure of ASST which recommends discontinuation of antihistamines and immune-suppressants at least 2-3 days and 2 months respectively. The procedure is as follows- withdraw 2 ml of venous blood, allow it to clot at room temperature, followed by centrifugation at 2000 rpm for 10-15 minutes to separate serum. Intradermal injection of 0.05mL of serum is given over volar aspect of forearm. Equal volume of negative control i.e. normal saline and positive control i.e. histamine (10 μg/mL) is also injected intradermally, at a gap of 3 to 5 cm, over volar aspect of the same forearm. After 30 minutes, the injected sites are assessed for wheal and flare. If the average of maximum diameter of serum-induced wheal response in horizontal and vertical dimension is more than 1.5 mm as compared to saline-induced response, then the test is considered as positive.[29]

As per Ghosh *et al*., the subset of population with a positive ASST is more likely to experience endogenous causes of urticaria. Additionally, a positive test correlates with the duration and severity of the disease.[29]

2. INFLAMMATORY BIOMARKERS

I. C-Reactive Protein (CRP):-

Several studies have highlighted the presence of elevated levels of CRP in patients of CSU as compared to HC. Kolkhir *et al*. demonstrated association of elevated levels of CRP with activity of urticaria, quality of life impairment, autologous serum skin test, and arterial hypertension in a cohort of CSU patients.[30] It's role as a marker for short duration of disease has been suggested.[25]

II. Interleukin 6 (IL-6):-

IL-6 is a proinflammatory mediator that drives immune and inflammatory responses via IL-6 sR (soluble receptor) and gp 130 (signal transducing membrane glycoprotein 130). Kasperska-Zajac *et al*. illustrated higher level of both IL-6 and its receptor IL-6 sR in patients of CSU. They also noted that levels of IL-6 parallels the levels of CRP. [31] It can be used to differentiate moderate/severe disease from mild disease and active phase from remission.[25,26]

III. Other inflammatory biomarkers:-

CSU patients show high levels of IL-17, IL-23 and TNF-α, all of which are proposed as potential biomarkers of disease activity. Levels of IL-18, IL-31 are elevated in CSU patients. Literature supporting association of IL-18 and disease activity of CSU is scarce. While in case of IL-31, no correlation has been found with disease activity.[26]

Lipocalin-2 (LCN2) is a pro-inflammatory adipokine, which is increased in CSU. Its higher levels show an inverse relation with disease activity and direct relation with response to antihistamine therapy. [25,26]

3. BIOMARKERS OF ANGIOGENESIS, COAGULATION AND VASCULAR DYSREGULATION

I. Vascular endothelial growth factor (VEGF):-

Angiogenesis not only affects physiological functions but also actively contributes in a number of pathological disorders like fibrosis, chronic inflammation, and tumour formation. Among various pro-angiogenic factors, vascular endothelial growth factor (VEGF) is the most potent one and is involved in chronic inflammatory diseases. Patients of CSU demonstrate new vessel formation in lesional skin that appears to be produced by locally present mast cells, basophils, eosinophils, neutrophils, and macrophages. High levels of VEGF in their tissue and circulation indicates its direct impact on both the development of new blood vessels and vascular leakage. It also has an effect on inflammatory cells leading to continuation and augmentation of inflammatory process.[26]

II. Endogenous anti-angiogenic mediators:-

Endostatin (ES) and thrombospondin1 (TSP-1) are endogenous anti-angiogenic mediators which lead to formation of wheals and flare by promoting vascular leakage. Their raised levels are encountered in patients of CSU. However, they are not recommended as a biomarker because they do not show any correlation to disease activity. [26]

III. Matrix metalloproteases 9 (MMP-9)

Both adult and paediatric patients show elevated levels of MMP-9 in peripheral blood. A number of inflammatory cells such as macrophages, mast cells, neutrophils and T cells secrete MMP-9 which drives the inflammatory process by contributing to migration and activation of immune cells. Association of plasma levels of MMP-9 with disease activity of CSU has been suggested. [26]

IV. Adhesion molecules

Intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) are leukocyte adhesion molecules which are markers of endothelial dysfunction. They augment vascular permeability leading to wheal formation. Soluble forms of these molecules are elevated in circulation as well as in skin biopsies of CSU patients. Endothelial-cadherin (sVE-cadherin) is a endothelial cell adhesion molecule which in higher levels correlates to severity of CSU.[26]

V. Products of coagulation and fibrinolysis

CSU involves activation of extrinsic coagulation pathway as well as secondary fibrinolysis. This translates as increased levels of prothrombin fragment 1+2 and D-dimer, which correlates with disease activity. D-dimer has recently been suggested as a marker of antihistamine resistance, omalizumab response, and a good tool to track clinical response to cyclosporine A (CsA). However, influence of comorbidities like chronic infections and autoimmune disorders, in increasing D-dimer level is yet to be ruled out. [26]

VI. Platelets

Raised platelet count and higher mean platelet volume (MPV) correlates with disease activity and severity of CSU. [26]

4. BASOPHIL COUNT AND ACTIVITY

According to Grattan *et al*., a decreased leukocyte count in the peripheral blood correlated with disease activity. The same group also reported a negative linear association between basophil counts and severity of disease in untreated patients of CSU. [32] It is most likely caused by the migration of these cells to lesional skin. Systemic steroids increase peripheral basophil count by inhibiting their recruitment into lesional skin. Therefore, therapy with systemic steroids reduces wheal formation.[25]

Aghdam *et al.,* in their study involving treatment of CSU patients with omalizumab, evaluated effect of the monoclonal antibody on various FcεRI-bearing leukocytes. Post treatment only basophil percentage documented a rise while other leukocytes showed stable counts.[6,33]

Johal *et al.* found that patients with reduced basophils in circulation at baseline had higher symptom scores and slower resolution of symptom with omalizumab as compared to those without it. This was consistent with earlier studies evaluating basopenia as a marker of disease severity.[11,34] Rijavec *et al.* also outlined insufficient response to omalizumab in patients harbouring very low peripheral blood basophils (1.7 basophils/μL). This low basophil count was also associated with reduced FcϵRI and IgE expression on basophils. This inverse relation of basophils with severity of CSU was noted with anti-histamine therapy also.[6,35]

CD203c is a surface marker of basophils which indicates activation of basophils and has been proposed as a marker of disease severity. After treatment with omalizumab, circulating basophils show enhanced expression of CD203c. It is likely due to migration of activated

basophils from skin to circulation. Few reports still recommend against use of CD203c expression as a guide to basophil activation.[6,25] Levels of basophil FcεRI decrease significantly after treatment with omalizumab.[25]

Oliver E. T. *et al*. conducted a study in 38 participants to compare the interval shifts between disease activity and basophil count. They reported that basophil count, measured indirectly by total blood leukocyte histamine content was lower during disease activity and the counts improved during disease remission. Moreover the histamine release by basophils during reduced disease activity correlated with the increases in blood basophil count.[36]

NOVEL MARKERS

Heat shock proteins 70 (Hsp 70) is hypothesized as a trigger for humoral as well as cell mediated immune response in CSU. Antibodies against this autoantigen activate pro-inflammatory pathways. Levels of both Hsp70 and anti-Hsp70 antibodies are higher in the plasma of patients with moderate-severe CSU, however its use as a biomarker is yet to be elucidated.[26]

Oxidative stress induces the release of pro-inflammatory cytokines and modulates enzymatic functions in the pathogenesis of CSU. Nettis *et al* reported significantly higher levels of advanced oxidation protein products in patients of CSU. On the contrary, similar results were not obtained for advanced glycation end products .[26,37]

Epigenetics: - miRNA can influence inflammation by inducing gene silencing. Five miRNAs namely- 2355–3p, 4264, 2355–5p, 29c-5p, and 361–3p have been detected at significantly higher levels in CSU patients and are proposed as biomarkers.[26]

Vitamin D determines susceptibility to autoimmune disorders by virtue of its immunomodulatory action. In a study by Woo *et. al.,* lower levels of Vitamin D were reported in acute urticaria and atopic dermatitis patients as compared to healthy controls (HC). In fact, an inverse relation between disease severity and duration and CSU was proposed.[25]

Table 1 shows various markers and their correlation with CSU[26]

TABLE 1: Various markers and their correlation with CSU[26]

Type of Markers	Markers
Disease activity	Basophil count CD203-c basophils CPR IL-6 IL-17, IL-23, TNF-a LCN2 Prothrombin fragment 1+2 D-dimer NSAIDs exacerbation ASST positivity
Disease course	IL-6 IgG anti-TPO Age Gender Angioedema Association with inducible urticaria NSAIDs exacerbation Metabolic syndrome Basophil FcεRI expression
Response to therapy	CPR IL-31 LCN2 D-dimer C5a ASST positivity BHRA positivity

QUALITY OF LIFE (QOL)

Although chronic urticaria does not produce long-term organ damage, it can still be severely debilitating and distressing and have a profound impact on quality of life (QoL). Impairment in QoL in CSU patients is comparable to that reported in patients anticipating coronary artery bypass surgery. Intense itching and unpredictability of urticarial lesions accounts for hindrance in daily activities thereby causing mental and emotional anguish. Patient's perspective on the effects of disease and treatment is given due importance through patient-reported outcome (PRO) measures, particularly if they are well validated.[13]

To evaluate QoL in CSU, a variety of indices and questionnaires (including both generic and specific to skin diseases) have been employed. A few of these are depicted in table 2. [39]

Table 2: Tools for assessing QoL in patients of Chronic Urticaria

Tools for assessing QoL in patients of Chronic Urticaria [39]
Generic questionnaires • Medical Outcomes Survey Short Form-36 (SF-36) • Medical Outcomes Survey Short Form-12 (SF-12) • Nottingham Health Profile (NHP) • Satisfaction Profile (SAT-P) • Euro-QoL • WHO QoL Assessment-Brief (WHOQOL-BREF) • Work Productivity and Activity Inventory (WPAI-AS)
Specific skin disease questionnaires • Dermatology Quality of Life Index (DQLI) • Children's Dermatology Life Quality Index (CDLQI) • Dermatology Quality Of Life Scales (DQOLS) • Dermatology-Specific Quality of Life (DSQL) • Skindex-29 • Skindex-16 • VQ-Dermato
Specific chronic urticaria questionnaires • Chronic Urticaria and Quality of Life Questionnaire (CU-Q2oL) • Urticaria Severity Score (USS)

1. URTICARIA ACTIVITY SCORE 7 (UAS7)

It is a self-assessment tool for tracking disease activity of urticaria and is recommended by EAACI/GA2LEN/EDF/WAO consensus guidelines. [40] It gauges itching and wheals from a score of 0 to 3, based on a Likert-type symptom intensity scale(table 3). Higher scores stand for severe intensity of itching and greater number of wheals. Both these scores sum up to make the total daily urticaria activity score which ranges from 0 to 6. The score can be recorded either daily or twice a day but once daily recording is preferred due to better compliance. Keeping with that, the weekly UAS lies between 0 and 42. This score can be documented during observation, therapy, and follow-ups. It is a validated tool, which has been used in numerous controlled trials and in clinical practice.[13,39]

TABLE 3 : Urticaria Activity Score [39]

Urticaria Activity Score		
Score	**Wheals or hives**	**Itch**
0	None	None
1	Mild (<20 wheals/24 h)	Mild
2	Moderate (21-50 wheals/24 h)	Moderate
3	Intense or severe (>50 wheals/24 h or large confluent areas of wheals)	Intense or severe

The interpretation of weekly urticaria activity score is done as given in table 4:-

TABLE 4: Interpretation of UAS7 [13]

Disease state	**UAS7 score**
Severe activity	28-42
Moderate activity	16-27
Mild activity	7-15
Well-controlled	1-6
Completely controlled	0

2. CHRONIC URTICARIA QUALITY OF LIFE QUESTIONNAIRE (CU-Q2oL)

The Chronic Urticaria Quality of Life Questionnaire (CUQ2oL) was developed to serve as an uncomplicated assessment tool for patients. The is the only validated index to assess disease-specific impairment in quality of life in patients with CSU.[13]

This questionnaire accurately represents health-related quality of life (HRQoL) in CU patients which is in accordance with the results of the CU-psychometric Q2oL's testing. It is significantly better as it contains elements chosen by patients(Table 5). Additionally, the validation methods have demonstrated that CUQ2oL is valid with strong internal consistency, responsiveness, reliability, and validity.[40]

It is easy to fill and takes about five minutes. The CU-Q2oL questionnaire can assist both in deciding treatment and monitoring response.[40]

Table 5: Modified CU-Q2oL questionnaire

Modified CU-Q2oL questionnaire.[41]	
Serial number	**Questionnaire**
1	Are you affected by itch?
2	Are you affected by wheals (welts)?
3	Are you affected by swelling (e.g. of lips or eyes)?
4	Urticaria interferes with my regular activities at home and at work.
5	Urticaria interferes with my recreational activities.
6	Does urticaria affect your sleep?
7	Do you have difficulty falling asleep?
8	Do you feel tired during the day because of your bad night sleep?
9	Does urticaria affect your mood?
10	Are you feeling irritable because of your symptoms?
11	Do you feel embarrassed because of your condition?
12	Are you embarrassed to go into public places?
13	Do you put limits on your food choices because of urticaria?
14	Do you put limits on your physical activity because of urticaria?
15	Are you affected by side effects from your medication?

The self-administered questionnaire comprises of four categories: - personal information, real-world issues, activities, and mood. The responses include: zero for not affected, 1 for

hardly affected at all, 2 for slightly affected, 3 for moderately affected, 4 for quite a bit affected, 5 for very affected, 6 for extremely affected.[41]

3. DERMATOLOGY LIFE QUALITY INDEX (DLQI)

It is a 10 item based dermatology specific questionnaire for patients aged 16 years and more (Table 6). Similarly, for patients aged between 4 to 16 years there is a child's version. Six categories of items are combined to create six independent scores. These items include- symptoms and feelings (item 1 and 2), daily activities (item 3 and 4), leisure (item 5 and 6), job and school (item 7), personal relationships (item 8 and 9), and treatment (item 10). The responses include "not at all," "a little," "a lot," and "very much" scored as zero, one, two, and three, respectively. Additionally, the "not relevant" response receives a score of zero. Item 7 is peculiar as it is composed of two parts. The "yes" and "no," responses in first part of item 7 are scored as 3 and 0, respectively; while "a lot," "a little," and "not at all," responses in the second part are scored as 2, 1, and 0, respectively. Thus, all 10 components have a value between 0 and 3. Missing values or values that are not applicable are recorded as zero.[13,42]

Adding up all the elements gives the total score that ranges from 0 to 30. Higher scores suggest greater QOL impairment.[42]

Table 6: Dermatology Life Quality Index.[42]

Dermatology Life Quality Index questionnaire[42]	
Serial number	**Questions**
1	During the past week, how itchy, sore, painful, or stinging has your skin been?
2	During the past week, how embarrassed or self-conscious have you been because of your skin?
3	During the past week, how much has your skin interfered with you going shopping or looking after your home or garden?
4	During the past week, how much has your skin influenced the clothes you wear?
5	During the past week, how much has your skin affected any social or leisure activities?

6	During the past week, how much has your skin made it difficult for you to do any sport?
7	During the past week, has your skin prevented you from working or studying? If no, over the last week, how much has your skin been a problem at work or study?
8	During the past week, how much has your skin created problems with your partner or any of your close friends or relatives?
9	During the past week, how much has your skin caused any sexual difficulties?
10	During the past week, how much of a problem has the treatment for your skin been, e.g., by making your home messy or by taking up time?

DIAGNOSIS

The history and presence of typical urticarial lesions, such as recurring itchy wheals, angioedema, or both for more than six weeks, is usually sufficient to make diagnosis of CSU. Reviewing photographs of wheals and angioedema taken by the patient during active episodes aids in diagnosis of CSU, as urticarial symptoms might not be present during physical examination. The main goal of the diagnostic workup is to verify the diagnosis of CSU.[44]

Patients presenting with unusual symptoms and/or symptoms, in addition to wheals and angioedema, require evaluation for alternative diagnosis. The same holds true for patients of CSU not responding to therapy. [44]

Recurrent wheals showing slower resolution / prolonged duration, association with fever or musculoskeletal pain should raise the suspicion of urticarial vasculitis (UV) and urticarial autoinflammatory diseases. In this context, a skin biopsy, laboratory tests like C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR) and/or complete blood count (CBC) with differential count are helpful. Rare diseases like Wells syndrome and hypereosinophilic syndromes also exhibit urticarial lesions, but they can be excluded by presence of long-lasting maculopapular lesions or plaques. A skin biopsy can be performed if there is a suspicion of bullous pemphigoid which may present without vesico-bullous lesions in early phase. [44]

Patients experiencing recurrent angioedema without wheals should be evaluated for bradykinin-mediated conditions such hereditary angioedema, acquired C1 inhibitor deficiency-induced angioedema, and angioedema caused by ACE inhibitors. Clues to thediagnosis comes from reviewing onset and duration of symptoms, presence of prodromal symptoms, abdominal angioedema, concomitant medication, response to anti-histamines and family history. Laboratory testing should include complement C4 levels, C1 inhibitor concentration and function in order to rule out hereditary angioedema caused by a C1 inhibitor deficiency. [44]

Since the cause(s) of urticaria remains elusive, appropriate testing for causative factor is not available. Detecting type I and type IIb autoimmunity in individuals with CSU involves measuring total IgE and IgG anti-TPO as well as, basophil testing if available. Certain factors like food, drugs, stress and infections (both viral and bacterial) can augment disease activity but routine testing is not advised. Coexistence of CIU with CSU is common and can be verified by history. For confirmation of CIU, a relevant provocation test may be advocated. [44]

Hashimoto's thyroiditis is the most common autoimmune condition with clinical effects on CSU. Therefore, all adult patients of CSU with concomitant autoimmunity, particularly Hashimoto's thyroiditis, should be assessed clinically along with measurement of IgG-anti-TPO and yearly thyroid function tests in positive asymptomatic individuals. Other associated comorbidities including allergic diseases and psychiatric disorders which must be assessed clinically. As per international recommendations, CRP and CBC with differential (blood basophil and eosinophil levels) should be done. D-dimer and total IgE levels measurements can assist in patient counselling regarding the course of disease and efficacy of treatment. [44]

HISTOPATHOLOGY

Urticaria is generally diagnosed based on clinical features so biopsy of urticarial lesions is not a routine practice. However, patients with severe, refractory urticaria or the one suspected to have an alternate diagnosis may be subjected to biopsy. Histopathological features of urticaria include minimal epidermal change with dermal edema and dermal perivascular and interstitial inflammatory cell infiltration. Both dermal edema and cellular infiltrate constitute the two major findings of urticaria, which demonstrate substantial heterogeneity. The dermal edema, appears as separation of collagen bundles. Urticaria features a mild perivascular cellular infiltrate, comprising of lymphocytes and few eosinophils. Occasionally interstitium may show mild infiltration of eosinophils as well as mast cells. Neutrophils infiltration can

also be seen in intravascular and perivascular location in early urticaria and physical urticaria.[45]

TREATMENT

Treatment of urticaria aims at treating the disease 'as effectively and as safely as possible', in order to achieve total control of disease and normalisation of quality of life. The therapeutic strategy for CU should involve-

a) Searching for and, if feasible, elimination of causal factors.
b) Decreasing disease activity by avoiding conditions that aggravate illness.
c) Induction of tolerance, lowering disease activity.
d) The use of medication to stop the release of mast cell mediators and/or their effects, which reduces the severity of the condition.[7]

Since the disease activity is prone to variations in activity, treatment should include 'treating as little as necessary' and 'as much as practicable'. This involves assessing, adapting, acting, and reassessing the patient to move up or down the treatment algorithm, based on the progression of the disease. It is crucial that patients should be effectively educated regarding ongoing care and use of patient-reported outcome (PRO) measures particularly UAS.[7]

Targeting mast cell mediators like histamine or activators like autoantibodies is the goal of current urticaria treatment regimens. Upcoming novel therapies are directed towards lowering the number of mast cells or silencing them with inhibitory receptors. All these symptomatic therapies aim to relieve patients' signs and symptoms unless spontaneous remission occurs. Pharmacological therapy should be continued until it is no longer required for control of disease.[7]

1. H1-ANTIHISTAMINES

The immunological response and allergic inflammation in urticaria is mediated by histamine and its four receptors- histamine 1 receptor to histamine 4 receptor (H1R-H4R). Among histamine receptors, H1-receptor promotes vasodilatation, cellular migration and nociception. H1antihistamines are inverse agonists that impede proper functioning of H1-receptors by maintaining them in inactive state.[46]

Efficacy of antihistamines in reducing itching is related to their activity against H1-receptor of afferent C nerve fibres. They reduce erythema by acting on cutaneous axon reflexes, and impede extravasation of plasma, immune cells and cytokines through action on the

endothelium of postcapillary venules that leads to reduced formation of wheals. Majority of antihistamines appear to exhibit anti-inflammatory properties, including a decrease in preformed and newly synthesized mediators, that consequently decreases recruitment of inflammatory cells and inflammation.[12]

At cellular level, antihistamine exert the following effects-

A. Stabilization of the basophil and mast cell membranes as well as suppression of calcium and intracellular cAMP transmembrane flux. This effect is caused by drug-membrane ionic interactions and not through H1 receptor.
B. H1 blockade impedes the action of cytoplasmic transcription factors such nuclear factor kappa-B (NF-kB), thereby preventing synthesis/release nitric oxide(NO), chemokines, cytokines, adhesion molecules.[12]

H1-antihistamines are classified into first and second-generation antihistamines. First generation H1-antihistamines interact with various types of receptors i.e. α-adrenergic, muscarinic, and serotonin receptors. Therefore, they are far less selective as compared to second generation H1-antihistamines. This limited receptor selectivity gives rise to adverse effects such as irritability, paradoxical excitation, hyperactivity, hallucinations, dry mouth, constipation, urinary retention and tachycardia. Further, first-generation H1-antihistamines pass the blood-brain barrier and act on H1-receptors present in central nervous system resulting in somnolence, tiredness, drowsiness, sedation, and headaches.[46]

Hence, use first-generation H1-antihistamines as first-line therapy of CU is not advisable due to their potentially serious adverse effects.[7]

On the other hand, few sgAH are selective inverse agonists at H1-receptors that do not traverse the blood brain barrier and cause minor or no sedation.[46]

Current international EAACI/GA²LEN/EuroGuiDerm/APAAACI guidelines, by Zuberbier *et al.* outlined a stepwise approach for the management of CSU. Second generation H1-antihistamines are recommended as first-line therapy. Recommended sgAH include cetirizine, levocetirizine, loratadine, fexofenadine, rupatadine, desloratadine, ebastine and bilastine . Doses of sgAH can be gradually increased to four times the standard dosage, without risk of significant adverse effects, until adequate response is achieved.[7]

Sarti L *et al*. analysed the efficacy and tolerability of up-dosing of sgAH in 67 paediatric patients diagnosed with CSU. The four fold dose of sgAH in the paediatric population was well tolerated. However, the efficacy was mostly limited to standard and double dose of antihistamines that was effective in majority of patients. Three & four fold doses were

associated with adverse effects. Few cases responded to Omalizumab while a subset of patients continued some or the other treatment on account of lack of remission.[47]

Iriarte Sotes P. *et al* reported increased efficacy of Levocetirizine, Cetrizine, Bilastine and Rupatadine with up-dosing. Fexofenadine at high doses also showed significant response. Adverse effects noted were drowsiness and headache.[48]

I. Levocetirizine

Levocetirizine is an L-enantiomer of cetirizine, possessing higher potency and similar tolerability as cetirizine. It is superior to placebo in controlling symptoms of urticaria.[49,50] Higher doses of levocetirize have been successfully and safely used in treatment of cholinergic and chronic spontaneous urticaria.Even from a cardiovascular standpoint, it is safe and suitable for updosing. Levocetirizine has a daily dosage recommendation of 5 mg.[12,50]

II. Bilastine

Bilastine belongs to benzimidazole-piperidine group of sgAH. Its recommended dose is 20 mg per day.[49] Bilastine exhibits moderate to high affinity and robust activity at H1-receptor while showing little affinity for other receptors, as per in-vitro research. Bilastine is effectively and quickly absorbed and undergoes minimal metabolism. It acts as a substrate for P-glycoprotein, which restricts its ability to cross the blood-brain barrier.[51] Up-dosing of bliastine is safe with minimal effects on cardiovascular system.[50] Bilastine has various advantages including prolonged duration of action, effectiveness, and lack of sedative effect on central nervous system.[51]

III. Fexofenadine

It is an active carboxylated derivative of terfenadine produced by CYP3A4 enzyme mediated oxidative N-dealkylation. Fexofenadine should be taken orally once daily at a dose of 180 mg, or twice daily at a dose of 60 mg. Godse *et al*. used higher doses of fexofenadine up to 540 mg/day for the treatment of urticaria and did not report any unfavourable cardiac effects.[50,52] Fexofenadine is generally well tolerated. Additionally, there is no cognitive or psychomotor impairment.[46]

The approved doses of various sgAH are given in table 7.[52]

Table 7: Approved doses of second-generation (non-sedating) antihistamines

Approved doses of second-generation (non-sedating) antihistamines[53]					
Drug	Adult dose	Dose adjustment	Pregnancy category	Grades of evidence	Strength of recommendation
Cetirizine	10 mg once daily	Hepatic or renal function impairment (CrCl<30ml/min/1.73m2)	B	1a	A
Levocetirizine	5 mg once daily	Dose adjustment is not necessary for patients with only hepatic impairment, but it should be considered in patients with both hepatic and renal impairment (CrCl<50 ml/min/1.73m2)	B	1a	A
Fexofenadine	180 mg once daily or 60 mg twice daily	Renal function impairment (CrCl<80 ml/min/1.73m2)	C	1a	A
Bilastine	20 mg once daily	Dose adjustment is not necessary for patients with both hepatic and renal impairments	B	1a	A
Desloratadine	5 mg once	Severe renal function impairment	C	1a	A

	daily	(CrCl<30 ml/min/1.73m2)			
Loratadine	10 mg once daily	Hepatic function impairment	B	1a	A
Rupatadine	10 mg once daily	Hepatic or renal function impairment (CrCl<30 ml/min/1.73m2)	B	1a	A

Grades of evidence	**Classification of strength of recommendation**	
1a Meta-analysis of RCTs 1b Single RCT 2a Systematic review of cohort studies 2b Single cohort studies and RCTs of limited quality 3a Systematic review of case-control studies 3b Single case-control study 4 Case series, case-cohort series or cohort studies of limited quality, expert committee opinion	Recommendation strength	Evidence grade
	A B C D	1a, 1b 2a, 2b, 3a, 3b 4 Expert opinion

Devillier P *et al* conducted a comparative review of pharmacokinetics of three sgAH i.e. Desloratadine , Fexofenadine and Levocetirizine and reported high affinity binding of all these drugs to H1 receptor, minimum effects on central nervous system, no major inhibition of Cytochrome P450, no clinically significant muscarinic effects and that all the 3 drugs were safe and effective in CSU.[54]

Podder I et al conducted a double blinded comparative study of Bilastine 20mg vs Levocetirizine 5 mg in a total of 58 patients and reported that both drugs were associated with improvement in CSU throughout the treatment period. The parameters assessed for disease activity were significant in the Bilastine group and quality of life did not show a significant difference between the two. However Bilastine was associated with a better

symptom control and lesser sedation as compared to Levocetirizine. The conclusion was that Bilastine can be used as an effective alternative to Levocetirizine. No major adverse effects were observed.[55]

2. OMALIZUMAB

Omalizumab is a recombinant, humanised, monoclonal antibody (mAb) targeting IgE. It is approved in patients of CSU who do not respond satisfactorily to sgAH. It is licenced for the management of CSU in patients aged 12 years or older.[7,56]

Treatment of CSU with omalizumab is both safe and effective. It significantly improves quality of life and suppresses development of wheals and angioedema. Omalizumab can be used for long-term control of urticaria. It can be started at a dose of 300 mg which is given at every four weeks. Patients who do not show improvement to this dosing regimen of omalizumab can receive treatment with greater dosages, shorter intervals or both. Studies suggest administration of omalizumab up to a maximum dose of 600 mg givenat every two weeks.[7]

3. CYCLOSPORINE

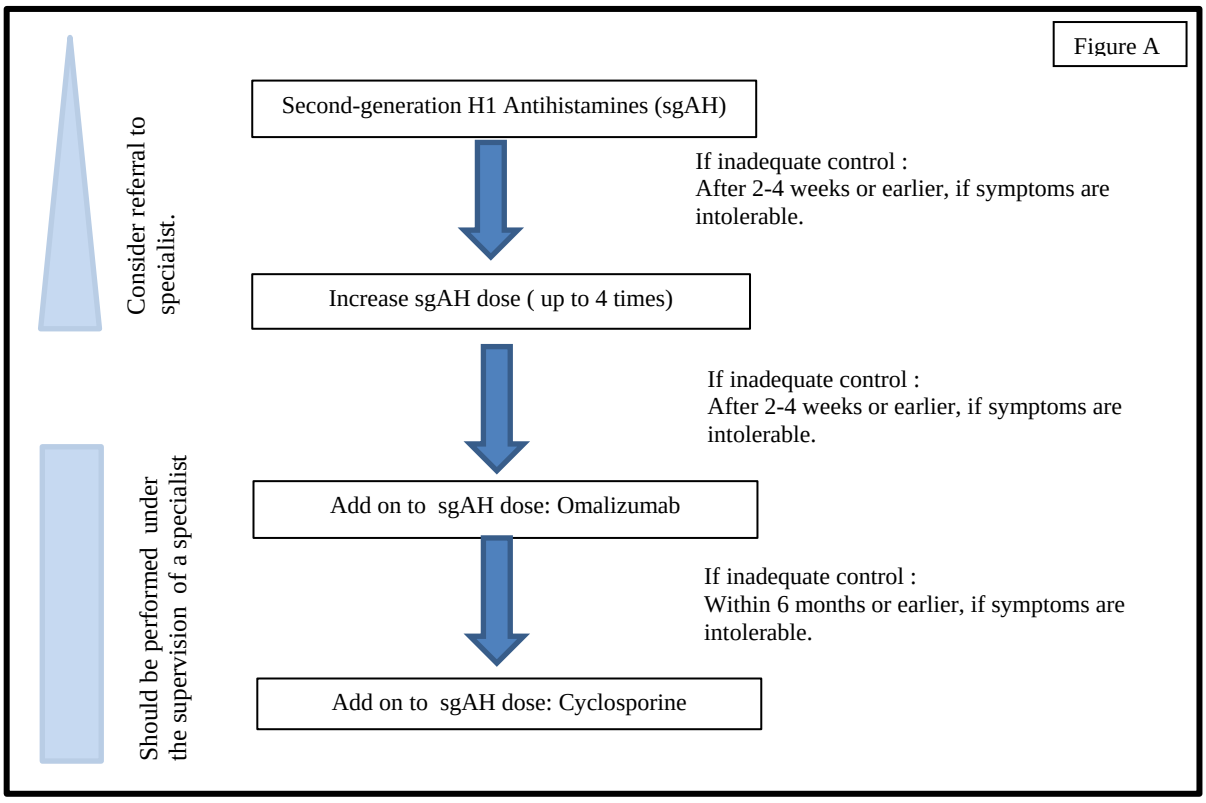
Cyclosporine suppresses the immune system and directly impacts the release of mast cell mediators. It is offered to patients who don not respond adequately to omalizumab. Its recommended dose ranges from 3.5 to 5 mg per kg bodyweight per day. It is an off-label drug for the treatment of urticaria that should only be used in patients with severe illness refractory to antihistamine and omalizumab alone. When compared to prolonged steroid treatment, cyclosporine offers a far superior risk/benefit ratio. [7]

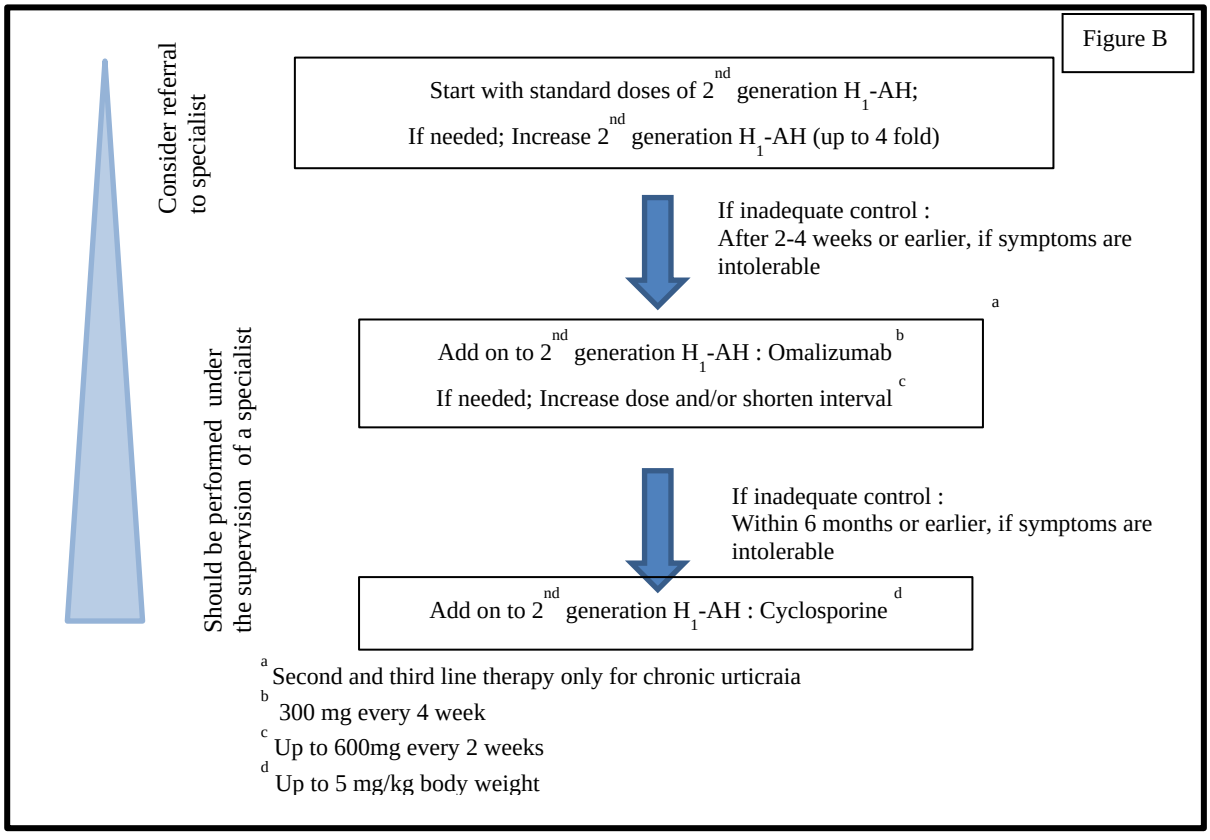
Zuberbier *et al* described a revised 3 step algorithm for the treatment of CSU. The old guidelines consisted of 4 steps i.e. initiating sgAH, escalating doses of sgAH, addition of omalizumab and addition of cyclosporine. The newer guidelines have merged the 1st and 2nd step of older one and included guidance regarding updosing and duration. Second, it instructs medical professionals to treat CSU using an “as much as needed and as little as possible” approach, depending on the degree of illness control determined by the Urticaria Control Test.[57] Table 8 shows the evidence in favour of use of omalizumab and cyclosporine in resistant cases of CSU.

Table 8: Agents for patients with chronic urticaria resistant to high-dose or combination antihistamine therapy.[58]

Agents for patients with chronic urticaria resistant to high-dose or combination antihistamine therapy[57]					
Alternative agent	**Typical dose**	**Onset of improvement**	**Estimated effectiveness**	**Evidence**	**Risk (pregnancy category)a**
Cyclosporine A	3–5 mg/kg/day	1–7 days	High	2 RCTs	Moderate-high (C)
Omalizumab	150–300 mg every 4 weeks	1–2 weeks	High	5 RCTs	Low-moderate (B)
a Category B: Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women; Category C: animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.					

Figures 1 A & B : Comparison of the treatment algorithms of the old (A) and new (B) versions of the international urticaria guideline. H1-AH, H1 antihistamine; LTRA, leukotriene receptor antagonist; sgAH, second-generation antihistamine.[56]





4. OTHER SYMPTOMATIC TREATMENTS

Systemic steroids: - A brief course of oral steroids for a maximum of 10 days may be offered for acute exacerbations of CSU for reducing disease duration or activity.

Phototherapy: - Treatment with UV-B, UV-A, and Psolaren UV-A therapy for an interval of 1 to 3 months can be added to antihistamine therapy for the treatment of CSU, while exercising due caution for its carcinogenic effects. [7]

Older guidelines have the supported use of dapsone and H2-antagonists but now there is insufficient evidence to support their inclusion in the algorithm. Nevertheless, they may still be relevant given their low cost in some healthcare systems.[7]

Other therapeutic methods including methotrexate, phototherapy, intravenous immunoglobulins (IVIG/IGIV), interferon and plasmapheresis have only case reports or low-quality evidence to support their use.[7]

Table 9 gives a comprehensive account of alternatives used in past for treatment of CSU.

Table 9: Other alternative treatments for CSU[59]

Other alternative treatments for CSU[59]					
Study	Drug	Study design	Number of patients	Treatment	Results
Pathania YS et al. 2019	Azathioprine	Prospective, randomized, active-controlled, noninferiority study	40	Starting dose 1 mg/kg/day in 2 divided doses + levocetirizine 10 mg/day for 90 days	32 out of 40 subjects achieved ≥ 75% reduction in using urticaria activity score
Tal Y et al. 2015		Retrospective, case series	2	Up to 150 mg/day + antihistamines	On remission during treatment
Bhanja DC et al.		Prospective, single blind,	26	50 mg/day + levocetirizine 5	Significantly lower total

2015		randomized control study		mg as needed for 8 weeks	severity score and fewer use of rescue antihistamine in treatment arm
Reeves GE et al. 2004	Chloroquine	Prospective, randomized, placebo-controlled study	9	Dose not specified, hydroxychloroquine + usual symptomatic urticarial therapies for 12 weeks	Significant improvements in the global symptom severity score and the LAMY-7. No significant difference in medication requirements or urticaria score.
Pho et al. 2011	Colchicine	Retrospective, chart Reviews	36	Most patients took 1.2 mg daily, treatment range 1-17 months	15 patients reported subjective clinical response, 5 patients reported partial response
Criado RF et al. 2008		Prospective, open study	9	1 mg daily	8 out of 9 patients achieved

					complete response after 12 weeks.
Asero R. 2005	Cyclophosphamide	Retrospective, case report	1	Oral, 1.5 mg/kg for 5 days/week + acetylcysteine 600 mg daily	Reported a 50% reduction of urticaria severity, allowed graduate discontinuation of prednisone use.
Bernstein JA et al. 2002		Retrospective, case report	1	IV, 500 mg Initially, followed by 100 mg increase every 2 weeks up to 1,500 mg once a month	Complete resolution of symptoms and discontinued prednisone within 7 months.
Raghavendran RR et al. 2014	Mycophenolate Mofetil	Retrospective, case report	1	500 mg twice daily + prednisolone 25 mg/day, gradually increased MMF dose to 1.5 g twice daily	Symptoms well-controlled, allowed discontinuation of prednisone.

Shahar E et al. 2006 Prospective, open-label, uncontrolled trial		Prospective, open-label, uncontrolled trial	9	1000 mg twice daily for 12 weeks	Reduction in the urticarial activity score, allowed discontinuation of prednisone.
Zimmerman AB et al. 2012		Retrospective, chart Review	8	500 mg twice daily initially, titrate up at 500 mg twice daily every 2 to 4 weeks	7 out of 8 subjects had improvement in urticaria, 3 out of 7 had complete control.

NEWER THERAPIES

Table 10 shows the newer therapies under trail for treatment of CSU.

Table 10: Licensed Drugs with Off-Label or Beyond-Label Use[56]

Licensed Drugs with Off-Label or Beyond-Label Use [56]	
Reslizumab, Mepolizumab, and Benralizumab:	IL-5 Targeting mAb
Dupilumab	Anti IL-4 and IL-13 mAb
Tranexamic Acid	Anti-fibrinolytic
Etanercept, Adalimumab, and Infliximab	TNF-a Inhibitors
Rituximab	Anti-CD20 mAb
Anakinra, Canakinumab, and Rilonacept	Anti IL-1 mAb
Abatacept	T-Cell costimulation modulator

MATERIALS & METHODS

MATERIALS AND METHODS

1. STUDY SETTING-

This study was conducted in patients of chronic spontaneous urticaria attending OPD at Department of Dermatology, Venereology and Leprology at All India Institute of Medical Sciences, Jodhpur.

2. STUDY DESIGN

An open-labelled, parallel design randomised interventional trial.

3. STUDY PARTICIPANTS

INCLUSION CRITERIA

Patients giving written informed consent and fulfilling the following criteria were included in the study.

- Patients with chronic spontaneous urticaria (clinically diagnosed).
- Duration of disease > 6weeks.
- Age ≥ 18 years and < 65 years.
- Treatment wash off period for H1 and H2 antihistamines is 3 days, for leukotriene receptor antagonist is 7 days and for systemic corticosteroids is 4 weeks.

EXCLUSION CRITERIA

Patients having any of the following criteria were excluded.

- Drivers and people working with heavy machinery.
- Ongoing treatment with Omalizumab or Cyclosporine A.
- Systemic illness like chronic liver disease or chronic kidney disease.
- Pregnancy and lactation.
- Known hypersensitivity to any of the drugs included in the study.

4. SAMPLING

The sample size was calculated using G power software v3.0^{TM}. Based on extensive literature search, there was a paucity of evidence to be considered as the base for sample size calculation.

So the sample size was calculated considering alpha error - 0.05, power - 90%, no. of groups- 3, effect size was assumed as 0.40. Sample size came out to be 84. After adding 10% attrition, the final sample size came out to be 93.

5. RANDOMIZATION AND ALLOCATION OF PARTICIPANTS

Computer generated randomization method was used to generate a table of random numbers, using which patient were randomly assigned to one of the three group. Allocation concealment was done with sequentially numbered opaque sealed envelopes (SNOSE). At the end of study, Group A consisted of 25 patients, Group B consisted of 32 patient and Group C had 27 patients.

6. STUDY DURATION

The study was approved by the Institutional Ethics Committee of All India Institute of Medical Sciences, Jodhpur vide certificate number AIIMS/IEC/2021/3300 dated 12th March 2021 and CTRI registration no. CTRI/2021/04/033119 dated 26 April 2021. Recruitment was started from May 2021 and patients were followed until October 2022.

7. ASSESSMENT

PRIMARY EFFICACY PARAMETER

Weekly Uricaria activity score (Annexure III) → recorded at each visit.

SECONDARY EFFICACY PARAMETERS

Basophil count→ recorded at baseline and at 6 weeks.

Chronic Urticaria-Quality of Life Questionnaire (CO-Q2oL) (Annexure V) → recorded at each visit.

Dermatology Life Quality Index (DLQI) (Annexure VI) → recorded at baseline and at 6 weeks.

8. STUDY PROCEDURE

Patients fulfilling the selection criteria were explained the objectives, methods and investigations included in the study and enrolled after obtaining a written informed consent. Clinical history was taken and examination was performed at baseline to confirm the diagnosis and alternative diagnosis were excluded. Following that, a pre-approved case sheet/ case proforma was filled which entailed demographic details, and other details pertaining to

the symptomatology, associations of the disease under study and past treatments. The primary efficacy parameter Weekly Urticaria Activity Score (UAS7) was analysed retrospectively for all patients and recorded at baseline and then at every follow-up visit. Similarly, impairment in quality of life produced by the disease was assessed using Chronic Urticaria-Quality of Life Questionnaire (CO-Q2oL) and Dermatology Life Quality Index (DLQI) and were duly recorded.

Total basophil count was recorded at baseline. Other relevant clinical investigation such as erythrocyte sedimentation rate, urine routine microscopy, stool for occult parasites, thyroid profile were performed and appropriate treatment was given for any anomalous result(s).

After documentation of all the baseline parameters, Patients were randomised into 3 therapeutic groups, with allocation concealment, using Research Randomiser Software$^{(TM)}$.

Group A received daily dose of oral Levocetirizine 5 mg at the start of study.
Group B received daily dose of oral Bilastine 20 mg at the start of study.
Group C received daily dose of oral Fexofenadine 180 mg at the start of study.

Quality of the drugs was assured by prescribing standard affordable brand(s) of the particular drug.

Follow-up was done at Day 14 and Day 28 or as per emergent need of the patient till 6 weeks. During the follow-up visits, appraisal of response to treatment, subjective improvement and adverse effects was done. Recording of UAS7 and CU-Q2oL questionnaire was done at every 2 weeks. Any patient failing to achieve adequate control and symptom relief was given a dose escalation based on based on EAACI/GA^{2}LEN/EDF/WAO GUIDELINES[40] (Subsequently there was an update and revision of the above mentioned guidelines vide Zuberbier T, Abdul Latiff AH, Abuzakouk M, Aquilina S, Asero R, Baker D, et al. The international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. Allergy. 2022;77(3):734-66). Any patient requiring more than fourfold dose escalation of sgAH was started on alternative therapy (namely cyclosporine, methotrexate or short course of systemic steroids) and were excluded from the study.

Final assessment for gauging treatment response was done at 6 weeks (Day 42) with UAS7, CU-Q2oL score and DLQI. The effect of these drugs on UAS7, CU-Q2oL score and DLQI at 6 weeks was compared with their baseline values to determine extent of disease control in the participants.

Similarly, assessment of Total Basophil Count was also done at 6 weeks which was compared with the initial recorded values.

The study concluded at 6 weeks; however, patients continued to receive treatment in accordance to their clinical condition.

9. COLLECTION OF BLOOD SAMPLES

Blood samples were collected immediately following evaluation. Venipuncture samples for the measurement of complete hemogram (CBC) and erythrocyte sedimentation rate (ESR) were collected in vials anti-coagulated with EDTA. Sample for TSH was collected in plain vial. Urine and stool samples were also collected and subjected to routine microscopic examination.

The pre-treatment and 6 week basophil counts were analysed and compared with UAS7.

10. LAB ANALYSIS

Complete blood count including basophils and the ESR were assessed using an automated haematological laser optical analyser (Sysmex-XN 1000). TSH levels were determined using an autoanalyser (Advia-centaur/ DiaSorin chemiluminescence assay). Urine and stool samples were analysed microscopically.

Figure 2: EDTA vial for blood sample collection.

Figure 3: Serum vial for blood sample collection.

Figure 4: SYSMEX XN-1000 Hematology Analyser

11. STATISTICAL ANALYSIS

Data was entered and analysed using Statistical Package for Social Sciences (SPSS) v.26.

Population Characteristics

Baseline characteristics of the patients were analysed using descriptive statistics. All variables were assessed for normality using Shapiro-Wilk test. Normally distributed data was represented as mean ± standard deviation. Non-normally distributed data was represented as median with inter-quartile range.

Comparison of parameters within groups

Wilcoxon signed rank test was applied to compare non-parametric variables at baseline and at end of study.

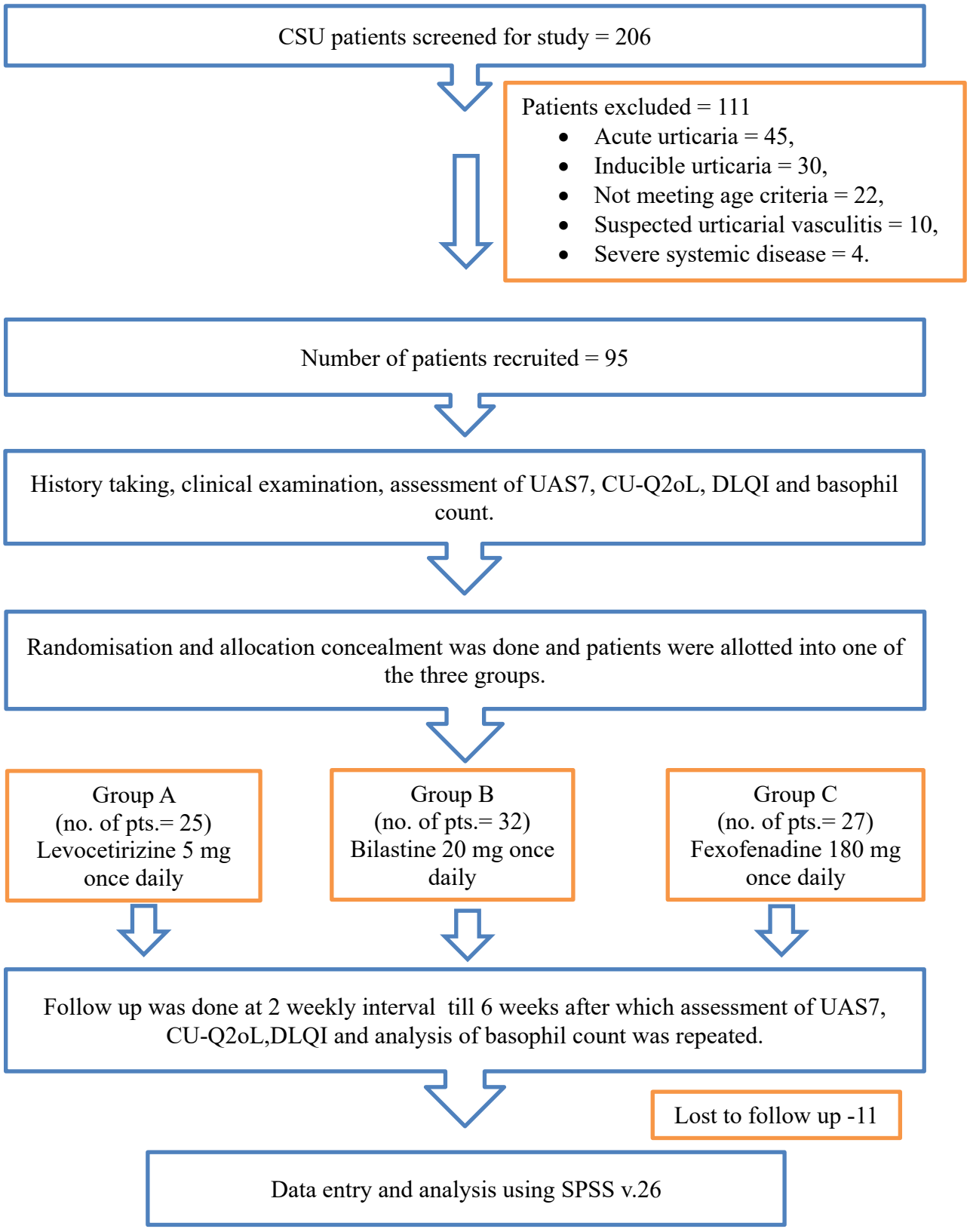
Comparison of parameters between groups

Categorical variables were analysed using the Chi-Square test. Parametric variables were analysed using one-way analysis of variance (ANOVA) test and non-parametric variables using the Kruskal Wallis Test.

Statistical Significance

P value < 0.05 was considered significant for all parameters.

Figure 5: CONSORT DIAGRAM



RESULTS

RESULTS

During the study period, 206 patients presented to the dermatology OPD at AIIMS, Jodhpur with chronic spontaneous urticaria. One hundred and one patients including patients with acute urticaria, inducible urticaria, severe systemic illness, suspected urticarial vasculitis and those not meeting age criteria were excluded. Following this 95 chronic spontaneous urticaria patients who gave their consent and met the selection criteria were recruited for the study. These patients were randomised and allocated into one of the three treatment arms. At the end of study period, 11 patients were lost to follow-up and 84 patients completed the study.

(A) DEMOGRAPHIC AND CLINICAL DATA

1. DEMOGRAPHIC CHARACTERISTICS

Age of the patients ranged from 18 to 65 years with a mean of 31.75 ± 10.78 years. There was a slight female preponderance [50 (59.5%)] with male: female ratio of 1:1.47. Education wise, the largest group was of graduates [39 (46.6%)]. The common occupations of recruited patients were homemakers [28 (33.3%)], students [20 (23.8%)] and businessman/women [11 (13.1 %)]. Eleven (13.1%) patients had a personal history of atopy. Seven (8.3%) patients had a family history of chronic urticaria. History of thyroid disorders was present in 4 (4.8%) patients.

Table 11: Demographic characteristics of patients (n= 84)

S. No.	Demographic characteristics	no. (%)
1	**Age**	
	18-20 years	13 (15.5)
	21-30 years	34 (40.5)
	31-40 years	15 (17.9)
	41-50 years	18 (21.4)
	51-60 years	4 (4.8)
	61-65 years	0 (0)
2	**Female**	50 (59.5)
3	**Education**	

	Illiterate	14 (16.7)
	Primary school	1 (1.2)
	Middle school	9 (10.7)
	High school	9 (10.7)
	Intermediate	11 (13.1)
	Graduate	39 (46.4)
	Postgraduate	1 (1.2)
4	**Occupation**	
	Student	20 (23.8)
	Homemaker	28 (33.3)
	Farmer	4(4.8)
	Businessman/woman	11 (13.1)
	Others (teacher, accountant, tailor, factory worker, policeman, etc.)	21 (25)
5	**History of atopy**	11 (13.1)
6	**Family history of urticaria**	7 (8.3)
7	**History of thyroid disorder**	4 (4.8)

Figure 6: Age Distribution of Patients

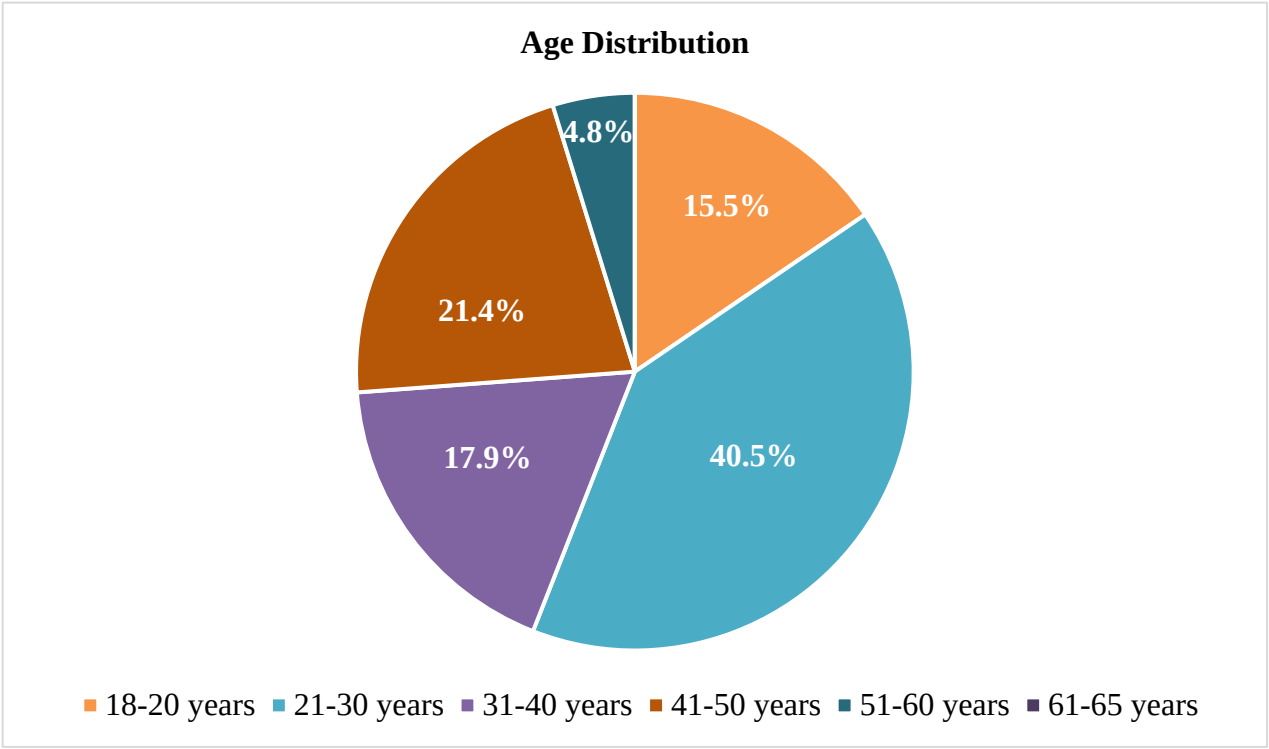
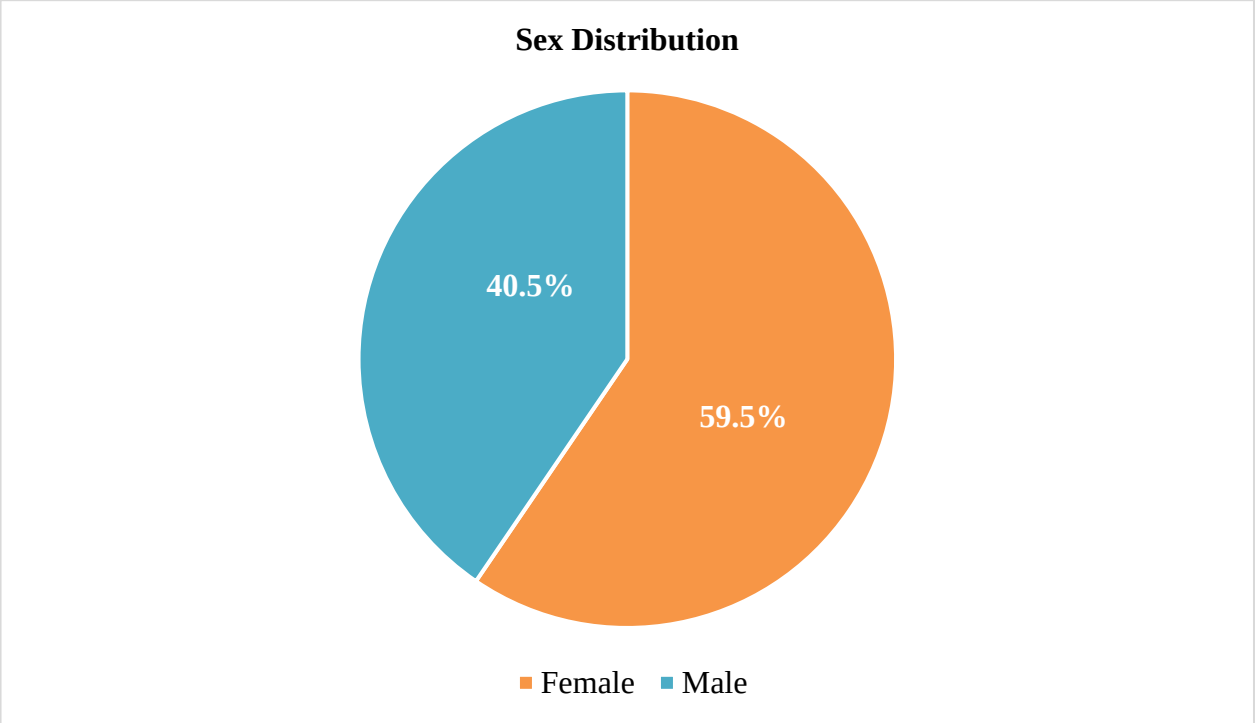


Figure 7: Sex Distribution of Patients



The mean age of patients in levocetirizine group was 33.28 ± 11.37 years, in bilastine group it was 32.75 ± 11.69 years followed by fexofenadine group where it was 29.15±8.83 years. A slight female preponderance was noted in all three (56%, 65.6% and 55.6%) groups. At baseline, the demographic characteristics of all the three groups were comparable.

Table 12: Comparison of demographic characteristics

S. No.	Demographic characteristic	Levocetirizine (no. of pts.= 25)	Bilastine (no. of pts.= 32)	Fexofenadine (no. of pts.= 27)	P-value
1	**Age (Mean ± SD)**	33.28 ± 11.37	32.75 ± 11.69	29.15±8.83	0.312*
2	**Female, [no. (%)]**	14 (56)	21 (65.6)	15 (55.6)	0.670†
3	**Education status [no. (%)]**				
	Illiterate	3 (12)	7 (21.9)	4 (14.8)	-
	Primary school	0 (0)	0 (0)	1 (3.7)	
	Middle school	2 (8)	4 (12.5)	3 (11.1)	
	High school	3 (12)	4 (12.5)	2 (7.4)	
	Intermediate	5 (20)	0 (0)	6 (22.2)	

	Graduate Postgraduate	12 (48) 0 (0)	16 (50) 1 (3.1)	11 (40.7) 0 (0)	
4	**Occupation, [no. (%)]**				
	Student Homemaker Farmer Businessman/woman Other (factory worker, policeman etc.)	5 (20) 9 (36) 0 (0) 2 (8) 9 (36)	6 (18.8) 9 (28.1) 2 (6.3) 0 (0) 15 (46.9)	9 (33.3) 10 (37) 2 (7.4) 0 (0) 6 (22.2)	-
5	**History of atopy,[no.(%)]**	3 (12)	4 (12.5)	4 (14.8)	-
6	**Family history of urticaria, [no. (%)]**	2 (8)	2 (6.3)	3 (11.1)	-
7	**History of thyroid disorder, [no. (%)]**	0 (0)	2 (6.3)	2 (7.4)	-
*- Analysis of variance (ANOVA) test †- Chi-square test					

2. CLINICAL CHARACTERISTICS

Disease duration showed wide variation ranging from 1.5 months to 20 years. The median duration of illness was 12 months [interquartile range (IQR) 4-34]. With regards to episodes of wheals it was noted that < 3 episodes per week were found in 32 (38.1%) patients, 3 -5 episodes per week in 14 (16.7%) patients and > 5 episodes per week in 38 (45.2%) patients. The distribution of wheals was ‘all over the body’ in 48 (57.1%) patients, over ‘limbs and trunk’ in 32 (38.1%) patients and less commonly over ‘limbs only’ [3 (3.6%)] and ‘limbs and face’ [1 (1.2%)]. Sixty-six (78.6%) patients had resolution of wheals within 6 hours while remaining [18 (21.4%)] patients had a duration of wheals lasting > 6 hours. Sixty (71.4%) patients reported a diurnal variation in occurrence of symptoms, out of which 44 (52.4%) patients reported maximum disease activity at night. In addition to wheals, 32 (38.1%) patients gave history suggestive of angioedema. Most patients [69 (82.1%)] were unaware of any triggering factor for their symptoms.

Table 13: Clinical characteristics of patients (n= 84)

S. No.	Clinical characteristics	Frequency
1	**Duration in months [Median (IQR)]**	12 (4-34)
2	**Episodes per week, [no.(%)]**	
	1-3/week	32 (38.1)
	3-5/week	14 (16.7)
	>5/week	38 (45.2)
3	**Duration of wheals, [no. (%)]**	
	< 6 hours	66 (78.6)
	6-24 hours	18 (21.4)
4	**Distribution of wheals, [no. (%)]**	
	All over the body	48 (57.1)
	Trunk and limbs	32 (38.1)
	Limbs	3 (3.6)
	Limbs and face	1 (1.2)
5	**Diurnal variation, [no. (%)]**	
	Day	16 (19)
	Night	44 (52.4)
	No variation	24 (28.6)
6	**History of triggering factors (as per patient), [no. (%)]**	15 (17.9)
7	**History of angioedema, [no. (%)]**	32 (38.1)

The mean duration of disease was found to be 22 ± 29.43 months in levocetirizine group, 31 ± 52.98 months in bilastine group and 25 ± 35.89 months in fexofenadine group. The frequency of wheals in levocetirizine, bilastine and fexofenadine group was noted as follows:- 1-3 episodes/week seen in 36 %, 34.4 % and 44.4 % patients respectively, 3-5 episodes/week in 12%, 18.8% and 18.5% patients respectively and > 5 episodes/week in 52%, 46.9% and 37% patients respectively. Majority of patients (76 %, 78.1 % and 81.5% respectively) in all 3 groups had resolution of wheals within 6 hours. History of angioedema was present in 36%, 43.8 % and 33.35% patients in levocetirizine, bilastine and fexofenadine group respectively.

Table 14: Comparison of clinical characteristics

S. No.	Clinical characteristics	Levocetirizine (no. of pts. = 25)	Bilastine (no. of pts. = 32)	Fexofenadine (no. of pts. = 27)	P-value
1	**Duration in months (Mean ± SD)**	23.22 ± 29.43	31 ± 52.98	25 ± 35.89	0.757*
2	**Episodes per week, [no. (%)]**				
	1-3/week	9 (36)	11(34.4)	12 (44.4)	0.814†
	3-5/week	3 (12)	6 (18.8)	5 (18.5)	
	>5/week	13(52)	15(46.9)	10 (37)	
3	**Duration of wheals, [no. (%)]**				
	< 6 hours	19 (76)	25 (78.1)	22 (81.5)	-
	6- 24 hours	6 (24)	7 (21.9)	5 (18.5)	
4	**Distribution of wheals, [no. (%)]**				
	All over the body	16 (64)	17 (53.1)	15 (27)	-
	Trunk and limbs	6 (24)	14 (43.8)	12 (44.4)	
	Limbs	2 (8)	1 (3.1)	0 (0)	
	Limbs and face	1 (4)	0 (0)	0 (0)	
5	**Diurnal variation, [no. (%)]**				
	Day	6 (24)	5 (15.6)	5 (18.5)	0.938†
	Night	13 (52)	17 (53.1)	14 (51.9)	
	None	6 (24)	10 (31.3)	8 (29.6)	
6	**History of triggering factors (as per patient), [no. (%)]**	4 (16)	6 (18.8)	5 (18.5)	0.959†
7	**History of angioedema, [no. (%)]**	9 (36)	14 (43.8)	9 (33.3)	0.691†
	* ANOVA test † Chi-square test				

3. EXAMINATION FINDINGS

At the time of presentation 28 (33.3%) patients had active wheals while in 22 (26.2%) patients dermographism was elicited.

Table 15: Examination findings of patients (n = 84)

S. No.	Examination findings	no.(%)
1	**Active wheals**	
	Present	28 (33.3)
	Absent	56(66.6)
2	**Dermographism elicited**	
	Yes	22 (26.2)
	No	62 (73.8)

Figure 8: Wheals noticed during examination of patients

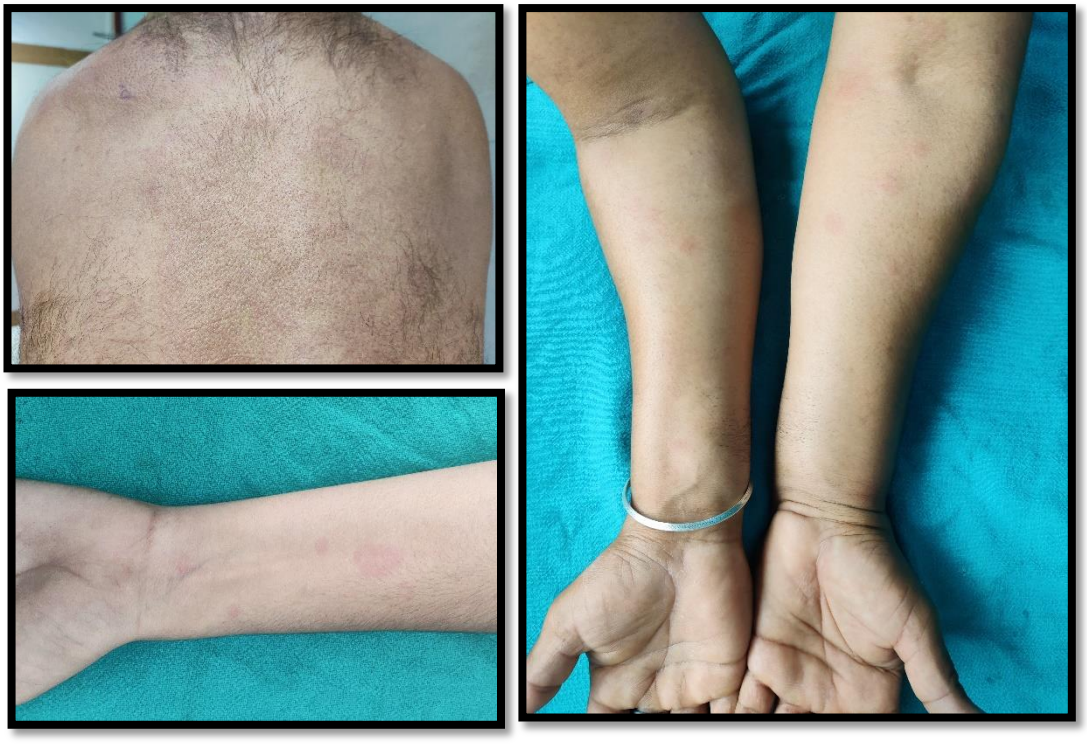
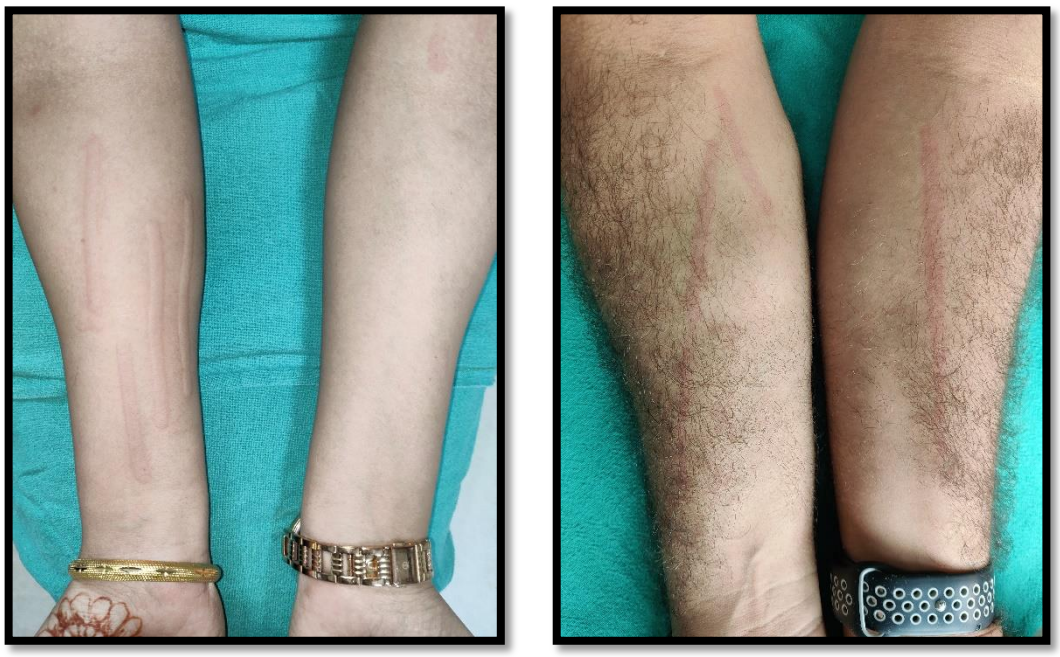


Figure 9: Dermographism elicited over forearm of patients



(B) <u>EFFICACY PARAMETERS</u>

1. <u>WEEKLY URTICARIA ACTIVITY SCORE (UAS7)</u>

UAS7 was assessed at every 2 weeks in all the three groups. The median (IQR) values of baseline UAS7 in Levocetirizine, Bilastine and Fexofenadine group were 20 (13.5-28), 21 (15-35) and 18 (12-28) respectively. The median (IQR) values of UAS7 calculated at 6 weeks in Levocetirizine, Bilastine and Fexofenadine group were 2 (0-4), 0 (0-5.75) and 0 (0-4) respectively.

With respect to weekly urticaria activity score, all the groups were similar in disease severity (UAS7) at baseline [p value = 0.427, Kruskal-Wallis Test].

All three groups showed significant reduction in UAS7 at 6 weeks of treatment when compared to baseline [p value (2-tailed) < 0.001 in all 3 groups , Wilcoxon signed rank test].

Inter-group comparison done utilising Kruskal-Wallis test revealed no statistically significant difference with regards to reduction in UAS7 across the three treatment groups (p value = 0.627).

Table 16: UAS7 at baseline

S. No	UAS 7 score at baseline (Severity)	Total (no. of pts.= 84)	Levocetirizine (no. of pts. = 25), [no. (%)]	Bilastine (no. of pts. = 32), [no. (%)]	Fexofenadine (no. of pts. = 27), [no. (%)]
1	0-6 (well controlled)	6 (7.1)	2 (8)	1 (3.1)	3 (11.1)
2	7-15 (mild)	25 (29.8)	7 (28)	10 (31.3)	8 (29.6)
3	16-27 (moderate)	24 (28.6)	8 (32)	8 (25)	8 (29.6)
4	28-42 (severe)	29 (34.5)	8 (32)	13 (40.6)	8 (29.6)

Table 17: UAS7 at 6 weeks

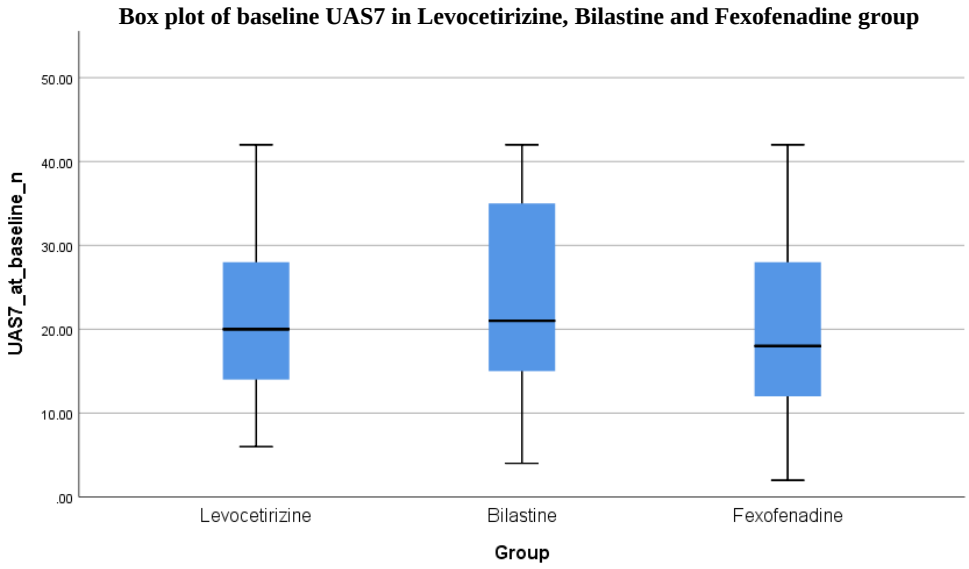
S. No	UAS 7 score at 6 weeks (Severity)	Total (no. of pts.= 84)	Levocetirizine (no. of pts. = 25), [no. (%)]	Bilastine (no. of pts. = 32), [no. (%)]	Fexofenadine (no. of pts. = 27), [no. (%)]
1	0-6 (well controlled)	71 (84.5)	22 (88)	25 (78.1)	24 (88.9)
2	7-15 (mild)	9 (10.7)	2 (8)	5 (15.6)	2 (7.4)
3	16-27 (moderate)	4 (4.8)	1 (4)	2 (6.3)	1 (3.7)
4	28-42 (severe)	0 (0)	0 (0)	0 (0)	0 (0)

Table 18: Comparison of UAS7 at follow-up

S. No	UAS7 at baseline	UAS7 at 2 weeks	UAS7 at 4 weeks	UAS7 at 6 weeks	P-value
Levocetirizine, Median (Interquartile range)	20 (13.5-28)	3 (1-14)	0 (0-4.5)	2 (0-4)	**<0.001**[¶]
Bilastine, Median (Interquartile range)	21(15-35)	5 (0.25-12)	0 (0-7)	0 (0-5.75)	**<0.001**[¶]
Fexofenadine, Median (Interquartile range)	18 (12-28)	6 (0-10)	0(0-6)	0(0-4)	**<0.001**[¶]
P value	0.427[#]	0.879[#]	0.816[#]	0.627[#]	

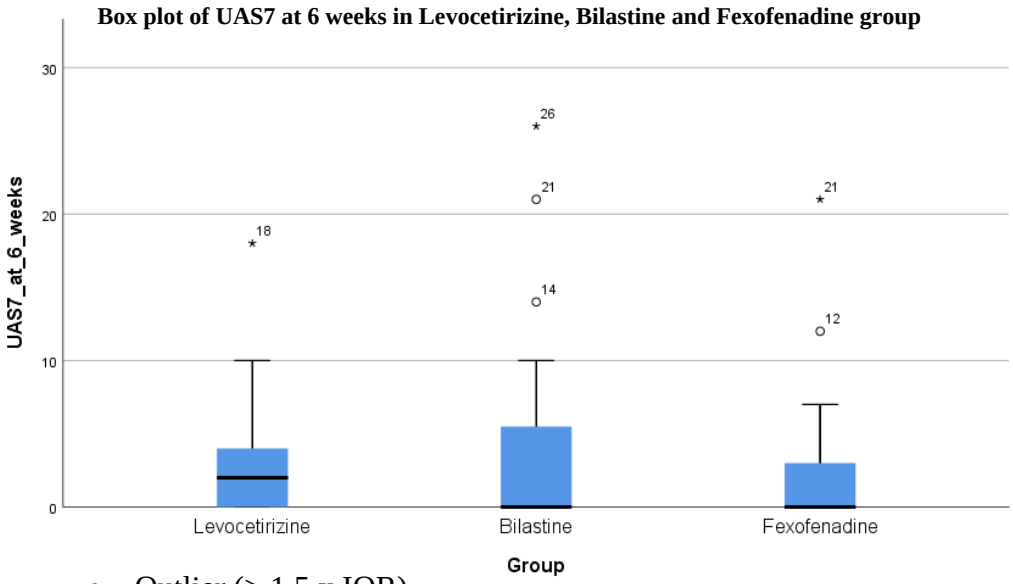
[¶] Wilcoxon signed rank test
[#] Kruskal-Wallis Test

Figure 10: Box plot of baseline UAS7 in Levocetirizine, Bilastine and Fexofenadine group



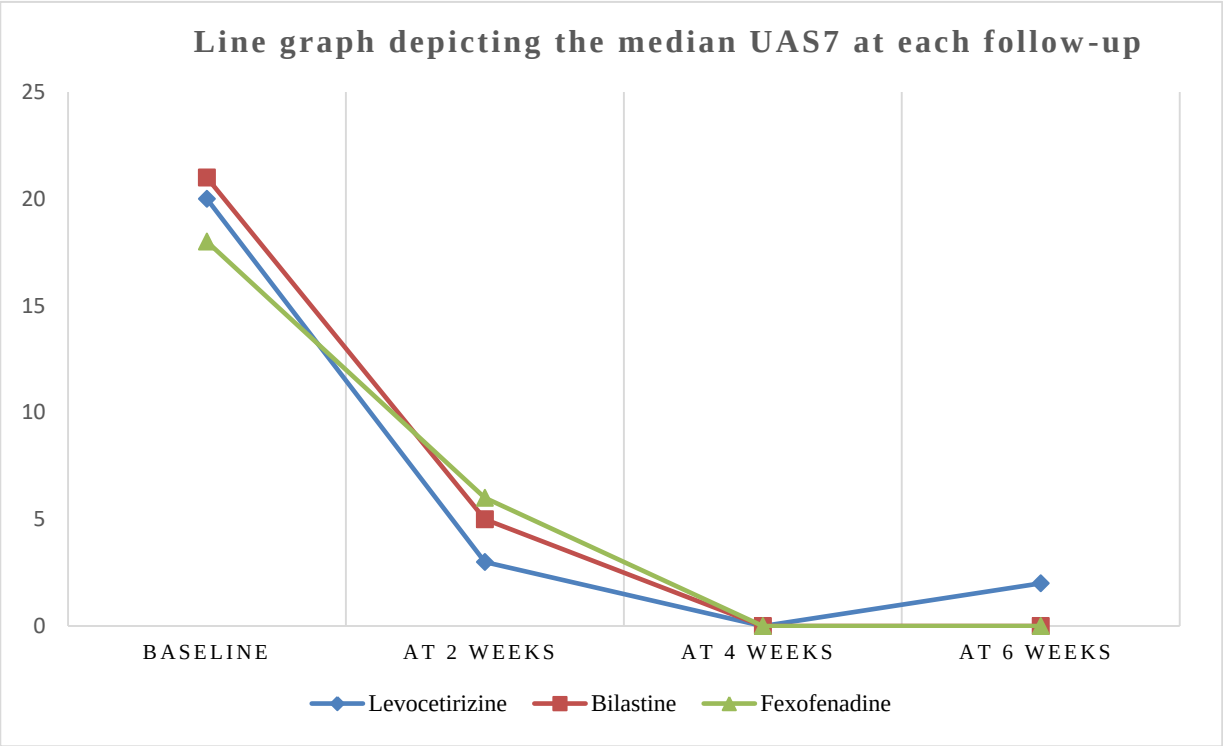
o – Outlier (> 1.5 x IQR)
* - Extreme outlier (> 3 x IQR)
Box – Interquartile range
Whisker – Minimum and maximum excluding outlier

Figure 11: Box plot of UAS7 at 6 weeks in Levocetirizine , Bilastine and Fexofenadine group



o – Outlier (> 1.5 x IQR)
* - Extreme outlier (> 3 x IQR)
Box – Interquartile range
Whisker – Minimum and maximum excluding outlier

Figure 12: Line graph depicting the median UAS7 at each follow-up



A significant decrease in UAS7 was noted in all groups at 2 weeks [p value (2-tailed) < 0.001, Wilcoxon signed rank test]. This difference prevailed between 2 and 4 weeks for levocetirizine and bilastine group [p value (2-tailed) <0.001,Wilcoxon signed rank test]. None of the groups showed significant reduction in UAS7 between 4 to 6 weeks [p value (2-tailed) = 0.165 , 0.589 and 0.099 for levocetirizine, bilastine and fexofenadine group, Wilcoxon signed rank test].

Table 19: Comparison of UAS7 scores at each follow-up

	UAS7 at baseline versus UAS7 at 2 weeks	**UAS7 at 2 weeks versus UAS7 at 4 weeks**	**UAS7 at 4 weeks versus UAS7 at 6 weeks**
	p value$^{\theta}$	p value$^{\theta}$	p value$^{\theta}$
Levocetirizine	**<0.001**	**<0.001**	0.165
Bilastine	**<0.001**	**<0.001**	0.589
Fexofenadine	**<0.001**	0.084	0.099
θ Wilcoxon signed rank test			

2. DOSE ESCALATION REQUIRED FOR DISEASE CONTROL

All patients were started on starting doses of a particular drug i.e. levocetirizine 5 mg once daily, bilastine 20 mg once daily and fexofenadine 180 mg once daily. However, dose escalation up to maximum of four times was done in patients with inadequate response, as per the international EAACI/GA^{2}LEN/EDF/WAO guidelines.[40]

The median (IQR) dose escalation required for disease control in Levocetirizine, Bilastine and Fexofenadine group were 2 (1-2), 1 (1-2.75) and 2 (1-2) respectively. On inter-group analysis, no significant difference was found between the doses required for disease control (p value = 0.768, Kruskal-Wallis Test).

Table 20: Distribution of dose escalation required for disease control.

S. No	Dose escalation	Levocetirizine [no. of pts. (%)]	Bilastine [no. of pts (%)]	Fexofenadine [no. of pts (%)]
1	1 time (standard dose)	11 (44)	19 (59.4)	13(48.2)
2	2 times	10 (40)	5(15.6)	12(44.4)
3	3 times	2 (8)	7 (21.9)	2 (7.4)
4	4 times	2 (8)	1 (3.1)	0 (0)

Table 21: Comparison of dose escalation required to achieve disease control

S. No	Dose escalation	Levocetirizine, Median (Interquartile range)	Bilastine, Median (Interquartile range)	Fexofenadine, Median (Interquartile range)	P-value
1	Median	2	1	2	0.768#
2	Interquartile range	1 - 2	1 - 2.75	1-2	
# Kruskal-Wallis Test					

3. BASOPHIL COUNT

Basophil count was assessed at baseline and after treatment at 6 weeks using an automated haematological laser optical analyzer (Sysmex-XN 1000). Median (IQR) values of basophil count at baseline in levocetirizine, bilastine and fexofenadine group were 20 (0-30), 20 (10-30) and 30 (10-40) respectively. Median (IQR) values of basophil count at 6 weeks levocetirizine, bilastine and fexofenadine group were 20 (10-40), 20 (10-30) and 20 (10-40)

respectively.

At the end of treatment, decrease in basophil count was noted in 4 (16%), 10 (31.3%), and 11 (40.7%) patients in levocetirizine, bilastine and fexofenadine group respectively. No change in basophil count was present in 11 (44%), 14 (43.8%) and 11 (40.7%) patients in levocetirizine, bilastine and fexofenadine group respectively. While an increase in basophil count was noted in 10 (40%), 8 (25%) and 9 (33.3%) patients in levocetirizine, bilastine and fexofenadine group respectively.

The difference in basophil count within the three groups at 6 weeks as compared to baseline was not significant [p value (2-tailed) = 0.092, 0.947 and 0.594 in levocetirizine, bilastine and fexofenadine group respectively; Wilcoxon signed rank test] No statistically significant difference was found on inter-group comparison using Chi-square test (p value = 0.262)

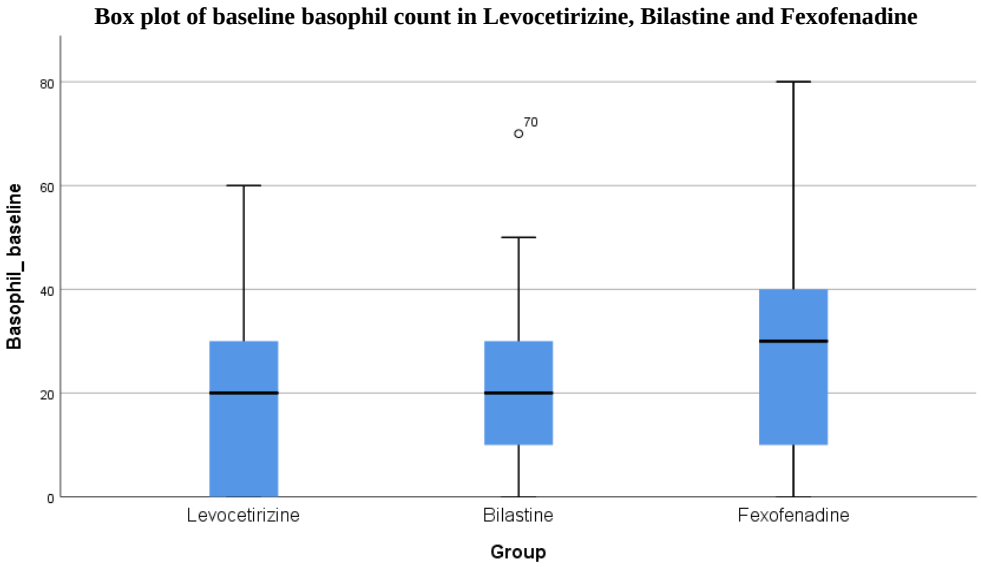
Table 22: Comparison of basophil counts at baseline and at 6 weeks

S. No	Basophil count	Levocetirizine, [Median (IQR)]	Bilastine, [Median (IQR)]	Fexofenadine, [Median (IQR)]
1	**Baseline**	20 (0-30)	20 (10-30)	30 (10-40)
2	**At 6 weeks**	20 (10-40)	20 (10-30)	20 (10-40)
	P value ¶	0.092	0.947	0.594
¶ Wilcoxon signed rank test				

Table 23: Comparison of change in basophil counts at baseline and at 6 weeks

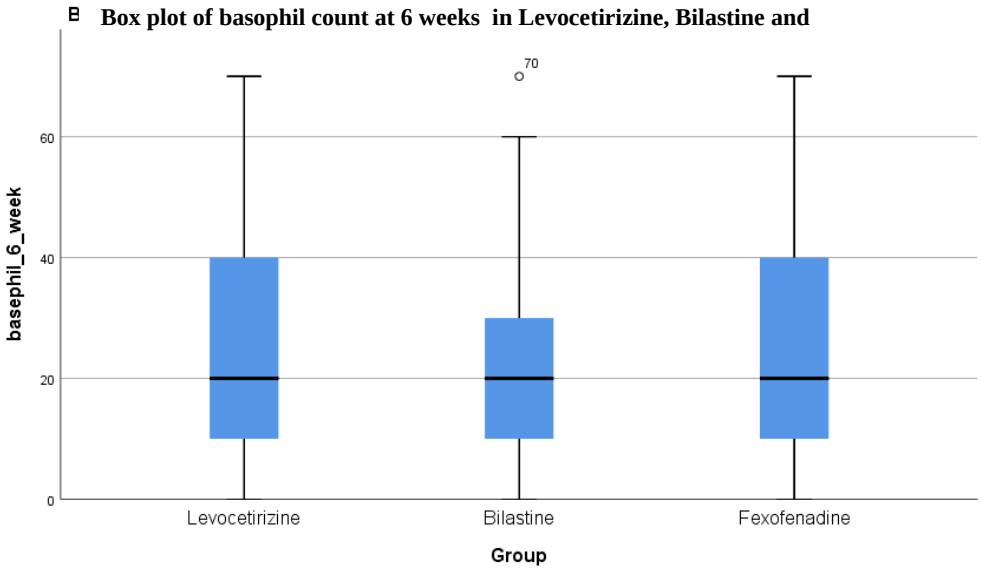
S. No	Variation in basophil count	Levocetirizine, No. of pts. (%)	Bilastine, No. of pts. (%)	Fexofenadine, No. of pts. (%)	P-value
1	Decrease	4 (16)	10 (31.3)	11 (40.7)	0.262†
2	No change	11 (44)	14 (43.8)	7 (25.9)	
3	Increase	10(40)	8 (25)	9 (33.3)	
† Chi-square test					

Figure 13: Box plot of baseline basophil count in Levocetirizine, Bilastine and Fexofenadine group.



o – Outlier (> 1.5 x IQR)
* - Extreme outlier (> 3 x IQR)
Box – Interquartile range
Whisker – Minimum and maximum excluding outlier

Figure 14: Box plot of basophil count at 6 weeks in Levocetirizine , Bilastine and Fexofenadine group



o – Outlier (> 1.5 x IQR)
* - Extreme outlier (> 3 x IQR)
Box – Interquartile range
Whisker – Minimum and maximum excluding outlier

4. <u>CHRONIC URTICARIA- QUALITY OF LIFE QUESTIONNAIRE (CU-Q2oL)</u>

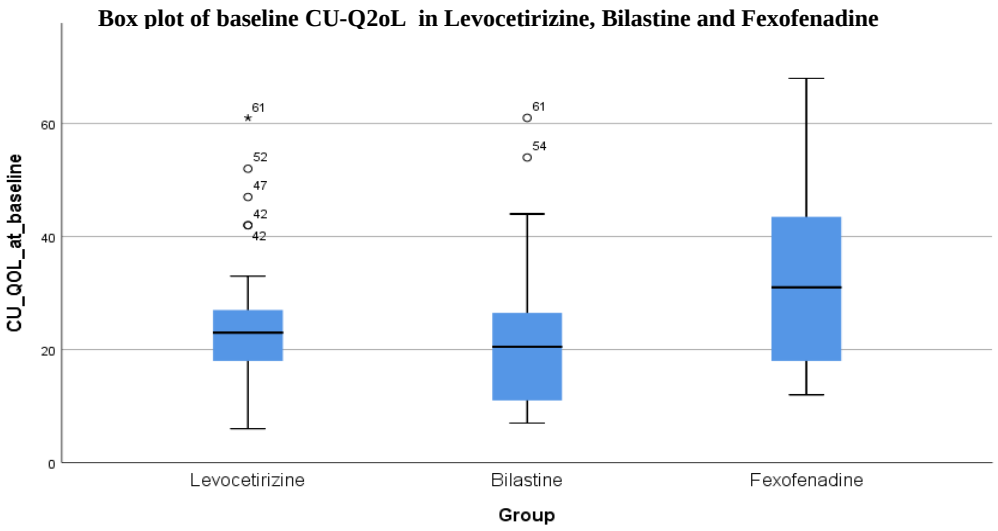
CU-Q2oL was evaluated at baseline and at 6 weeks in the three groups. Median (IQR) values of CU-Q2oL at baseline in levocetirizine, bilastine and fexofenadine group were 23 (17.5-30), 20.50 (11-27.25) and 31 (18-44) respectively. Median (IQR) values of CU-Q2oL at 6 weeks in levocetirizine, bilastine and fexofenadine group were 0 (0-3.5), 0 (0-2) and 0 (0-3) respectively.

Baseline CU-Q2oL score showed a statistically significant difference (p value =0.016, Kruskal Wallis test) among three groups. When compared from the baseline, all three groups showed statistically significant reduction in CU-Q2oL scores at 6 weeks [p value (2-tailed) <0.001 for all groups ,Wilcoxon signed rank test]. Kruskal-Wallis test used for inter-group analysis revealed no statistically significant difference between the scores at 6weeks(p value= 0.853).

Table 24: Comparison of CU-Q2oL at baseline and at 6 weeks.

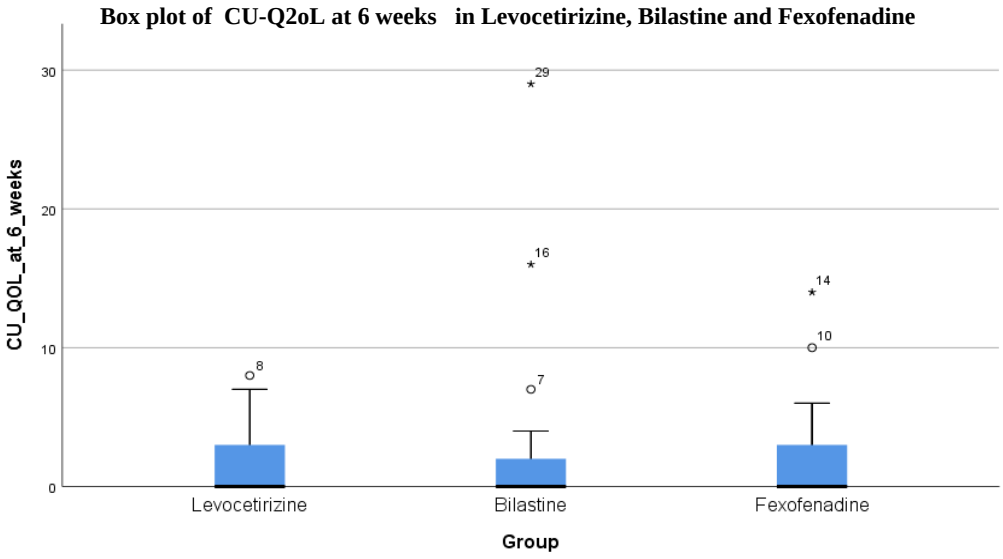
S. No	**CU-Q2oL**	**Levocetirizine, Median (Interquartile range)**	**Bilastine, Median (Interquartile range)**	**Fexofenadine, Median (Interquartile range)**	**P-value**
1	Baseline	23 (17.5-30)	20.50 (11-27.25)	31 (18-44)	**0.016**[#]
2	At 6 weeks	0 (0-3.5)	0 (0-2)	0 (0-3)	0.853[#]
	P value [¶]	**< 0.001**	**< 0.001**	**< 0.001**	
# Kruskal-Wallis Test ¶ Wilcoxon rank sum test					

Figure 15 : Box plot of baseline CU-Q2oL in Levocetirizine, Bilastine and Fexofenadine groups



o – Outlier (> 1.5 x IQR)
* - Extreme outlier (> 3 x IQR)
Box – Interquartile range
Whisker – Minimum and maximum excluding outlier

Figure 16: Box plot of CU-Q2oL at 6 weeks in Levocetirizine, Bilastine and Fexofenadine group



o – Outlier (> 1.5 x IQR)
* - Extreme outlier (> 3 x IQR)
Box – Interquartile range
Whisker – Minimum and maximum excluding outlier

5. DERMATOLOGY LIFE QUALITY INDEX (DLQI)

DLQI was analysed at baseline and at 6 weeks in the three groups. Median values of baseline DLQI in levocetirizine, bilastine and fexofenadine group were 5 (4-8), 4.5 (3-7.5) and 7 (5-10) respectively. Median values of DLQI at 6 weeks in levocetirizine, bilastine and fexofenadine group were 0 (0-0), 0 (0-0.75) and 0 (0-1) respectively.

Baseline DLQI showed a statistically significant difference (p value = 0.007; Kruskal wallis test) among the groups. There was statistically significant difference in DLQI score in all the groups when compared between baseline and at 6 weeks [p value (2-tailed) <0.001 for all groups ,Wilcoxon signed rank test]. Kruskal-Wallis test used for inter-group analysis revealed no statistically significant difference between the scores at 6 weeks (p value = 0.236).

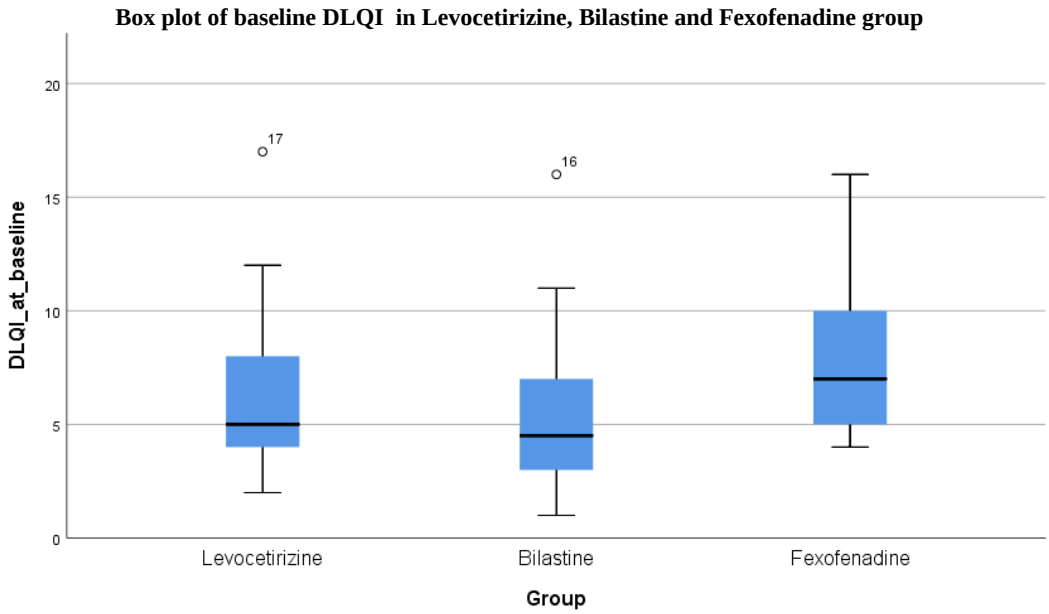
Table 25: Comparison of DLQI at baseline and at 6 weeks.

S. No	**DLQI**	**Levocetirizine, Median (Interquartile range)**	**Bilastine, Median (Interquartile range)**	**Fexofenadine, Median (Interquartile range)**	**P-value**
1.	Baseline	5 (4-8)	4.5 (3-7.5)	7 (5-10)	**0.007**[#]
2.	At 6 weeks	0 (0-0)	0 (0-0.75)	0 (0-1)	0.236[#]
3.	P-value[¶]	**<0.001**	**<0.001**	**<0.001**	

Kruskal-Wallis Test

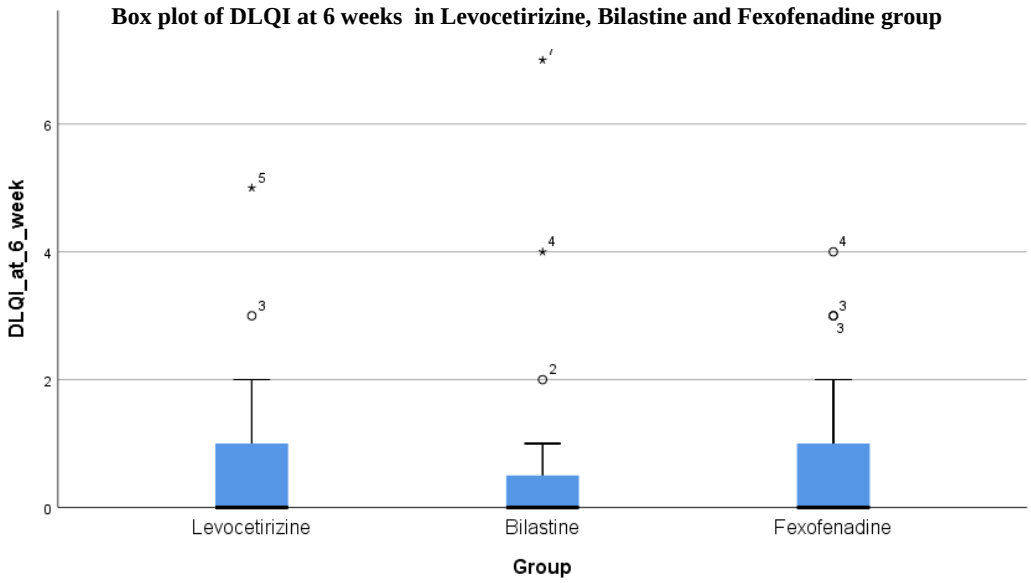
¶ Wilcoxon rank sum test

Figure 17: Box plot of baseline DLQI in Levocetirizine, Bilastine and Fexofenadine group



o – Outlier (> 1.5 x IQR)
* - Extreme outlier (> 3 x IQR)
Box – Interquartile range
Whisker – Minimum and maximum excluding outlier

Figure 18: Box plot of DLQI at 6 weeks in Levocetirizine, Bilastine and Fexofenadine group



o – Outlier (> 1.5 x IQR)
* - Extreme outlier (> 3 x IQR)
Box – Interquartile range
Whisker – Minimum and maximum excluding outlier

(C) <u>SIDE EFFECTS</u>

The side effects were recorded in all groups at each follow up. Sedation was the only side-effect noted i.e., 16 % patients in levocetirizine group, 12.5% patients in bilastine group and 14.8% patients fexofenadine group. None of the patients experienced headache, dry mouth, dry eyes, nausea, vomiting, diarrhea, constipation, anorexia and hypersensitivity.

Table 26: Comparison of side effects among treatment groups

S. No.	Side-effects	Levocetirizine, [No. of pts. (%)]	Bilastine, [No. of pts. (%)]	Fexofenadine, [No. of pts. (%)]
1	Sedation	4 (16)	4 (12.5)	4 (14.8)
2	Headache	0 (0)	0 (0)	0 (0)
3	Dry mouth	0 (0)	0 (0)	0 (0)
4	Dry eyes	0 (0)	0 (0)	0 (0)
5	GI adverse effects (nausea, vomiting, diarrhoea, constipation, anorexia)	0 (0)	0 (0)	0 (0)
6	Hypersensitivity reactions	0 (0)	0 (0)	0 (0)

DISCUSSION

DISCUSSION

Ninety-five patients with chronic spontaneous urticaria were recruited from Dermatology, Venereology and Leprology OPD at AIIMS, Jodhpur between May 2021 to October 2022 as per selection criteria. Patients were randomised and allocated into three groups i.e., Levocetirizine, Bilastine and Fexofenadine. Eighty-four patients completed the study and 11 patients were lost to follow-up. Out of the 84 patients, 25 patients were in Levocetirizine group, 32 patients in Bilastine group and 27 patients belonged to Fexofenadine group respectively.

The age of patients ranged from 18 to 65 years with a mean age of 31.75 ± 10.78 years. Majority of patients were in their 3rd decade of life [34 (40.5%)], followed by the 5th decade of life [18 (21.4%)] and thereafter the 4th decade [15 (17.9%)]. Thirteen (15.5%) patients were in age group of 18-20 years while 4 (4.8%) patients were older than 50 years. These findings were in concurrence with a study by Joseph *et al.*[60] on the epidemiology of chronic spontaneous urticaria in Indian population. They reported a mean age of 31.2 ± 20.7 years. In their study the largest proportion of patients were in their 3rd and 4th decade that accounted for 34.8% patients. A study from China reported mean age of 34.7±13.8 years. [61] Our data was in discordance with studies by Lapi *et al.* [62] (from Italy) and Danilycheva *et al.* [63] (AWARE study from Russia). The disparity in age distribution may be attributed to racial dissimilarity and to relatively younger population in India.

There was a slight female preponderance in our study with 50 (59.5%) patients being females and 34 (40.5%) patients being males. Similar findings were noted by Zhong *et al.*[61] wherein 59.3% patients were females. Higher female prevalence in patients of CSU has also been reported by Danilycheva *et al.*[63] (78.2%) and by Kulthanan *et al.*[53] (80%).

Personal history of atopic disorders like allergic rhinitis or bronchial asthma was noted in 11 (13.1%) patients in our study. This incidence was in contradiction to previous studies where higher numbers were reported. Vikramkumar *et al.*[28] had reported a history of atopy in 43.75% of CSU patients. In a study conducted in South Korea, Kim *et al.*[64] reported that around 80% patients of CSU had allergic rhinitis and nearly 40% had bronchial asthma. These variations may be attributed to the differential prevalence of atopy in different regions.

In our study, seven (8.3%) patients had a family history of urticaria. Joseph *et al.*[60] reported this in 8 (7%) patients, which was similar to our study. With respect to history of thyroid

disorders, a prevalence of 4.85% was noted in our study. This was in contrast to findings noted by Kim *et al.*[64] who reported thyroid disorders in 11.34% of CSU patients.

Duration of disease in our study varied between 1.5 months to 20 years with a median of 12 months. Around 39.3% patients had disease duration of less than 6 months. Disease duration ranging between 6 months to 12 months was noted in 5.9% patients, between 12 months to 60 months in 42.9% patients and greater than 60 months in 11.9 % patients. Our data is in concordance with the following studies. In the study by Vikramkumar *et al.*[28] the duration of disease ranged from 2 months to 10 years and the median duration was 12 months. Zhong *et al.*[61] reported that majority of the patients (72.6%) had a disease duration of < 6 months, followed by 18.4% patients with duration of 6-24 months, 13.1% having duration > 60 months and the least (8.4%) having disease for 24 to 60 months.

Sixty (71.4%) patients in our study reported diurnal variation in symptoms with predominantly nocturnal episodes in majority of patients [44 (5.2%)]. Zhong *et al.*[61] also reported primarily nocturnal symptoms in their patients (60%).

In our study, 32 (38.1%) patients had angioedema in addition to wheals. This finding was concordant to studies by Zhong *et al.*[61] (28.8%), Kulthanan *et al.*[53] (34%), and Maurer *et al.*[65] (45.5%). Our data was discordant with the findings of Joseph *et al.*[60] (7.8%), and Vikramkumar *et al.*[28] (66.6%).

In our study, dermographism could be elicited in 22 (26.2%) patients. This was consistent with findings of Joseph *et al.*[60] who reported dermographism in 23.9% patients and at variance with findings of Kulthanan *et al.*[53] (52%).

Our study assessed the clinical response through change in UAS7 which is a self-assessment tool recommended as per EAACI/GA^{2}LEN/EDF/WAO consensus[40.] At the end of 6 weeks, a statistically significant decline in UAS7 was noted across all groups [p value < 0.001, Wilcoxon signed rank test]. On comparing the decline in UAS7 at follow-up visits, all treatment groups showed statistically significant decline after 2 weeks of starting treatment. This statistically significant decline was maintained at week 4 in levocetirizine and bilastine groups. All groups had established maximum response by 4 weeks of treatment as no statistically significant change was noted in UAS7 between 4th and 6th weeks. This predictable declining trend across all treatment arms is consistent with the findings by Nettis *et al.* [49] (Levocetirizine 5mg), Hide *et.al.*[66] (Bilastine 20mg) and Kaplan *et al.*[67] (Fexofenadine

180mg) in controlling symptoms of urticaria although it must be pointed out that these trials were placebo controlled. Our findings are similar to study carried out by Shah *et al* [68]which also compared three drugs as used in our study.

On comparing response to treatment by UAS7, inter-group analysis revealed that none of the treatment was significantly superior to the other [p value = 0.627, Kruskal-Wallis test]. Our findings are in agreement with those by Shah *et al.*[68] who reported no statistically significant difference between bilastine, levocetirizine and fexofenadine in CSU. Zuberbier *et al.*[69] reported similar efficacy of levocetirizine and bilastine in controlling CSU, both being significantly superior to placebo. In a study comparing the efficacy bilastine with fexofenadine after two weeks of treatment in CSU, no significant difference was noted.[70] However, there are few studies demonstrating superiority of one sgAH when compared to the other . Podder *et al.*[55] compared bilastine 20mg with levocetirizine 5mg in patients of CSU and reported that bilastine was superior to levocetirizine in reducing UAS7. Godse *et al.*[71] reported significantly better control in CSU with fexofenadine as compared to levocetirizine when analysed at 4 weeks of therapy.

In our study, dose escalation to a maximum of 4 fold was done at each follow-up visit in patients with inadequate symptom control. Up-dosing was done in all groups and resulted in better control of symptoms. After up-dosing as per guidelines[40], control in CSU was noted in additional 44%, 31% and 40% patients in levocetirizine, bilastine and fexofenadine group respectively. On comparing the up-dosing required to achieve disease control in patients with inadequate response, no statistically significant difference was found between the three treatment groups (p value = 0.768, Kruskal wallis test). To the best of our knowledge, there are only a few studies that have evaluated the effect of up-dosing of antihistamines in CSU. Weller *et al.*[72] studied the effect of up-dosing of bilastine in patients of moderate to severe CSU and found that it helps in controlling symptoms in majority of cases. In a comparative study of bilastine versus fexofenadine by Shah *et al.*[70], up-dosing resulted in increased control of urticaria. Similar findings with up-dosing in levocetirizine and desloratidine were reported by Staevska *et al.* [73]

Our study also assessed change in basophil count after treatment with antihistamines. The change in basophil count at baseline and at 6 weeks was not found to be statistically significant (p value = 0.262 , Chi-square test). Inter-group comparison of change in basophil count did not show any significant results across the treatment groups Basophils play an

integral role in the pathogenesis of CSU. Studies have associated low peripheral basophil count with disease activity and increase in peripheral basophil count after treatment of CSU.[26] Saini *et al.*[74] reviewed trials on omalizumab in CSU and compared the effect of treatment on basophil percentage. Individual trials did not yield significant results but when combined showed significant increase in basophil percentage at 12 weeks. Kishimoto *et al.*[75] reported lower basophil count in their patient during phases of severe disease activity which reversed on treatment with omalizumab and relapsed on stopping treatment. Change in basophil count on treatment with omalizumab has also been extrapolated to antihistamines but there are not many studies that compare change in basophil count on treatment with the latter. Our study is apparently one of the firsts to observe the basophil counts before and after treatment with antihistamines in CSU.

We have also attempted to assess the impact of treatment on quality of life in patients of CSU utilizing CU-Q2oL and DLQI. At 6 weeks, all treatment groups showed significant reduction in CU-Q2oL scores from baseline [p value < 0.001, Wilcoxon signed rank test]. On inter-group comparison, CU-Q2oL scores were comparable in all treatment groups at 6 weeks. Similar reduction in CU-Q2oL scores were noted from baseline with bilastine and fexofenadine by Shah *et al* [70] However in their study, on comparing the reduction in CU-Q2oL scores, bilastine was found to be significantly superior to fexofenadine. Similar findings were noted in another study where bilastine, fexofenadine and levocetirizine were compared and statistically significant reduction in CU-Q2oL scores was noted in bilastine group.[76]

Assessing quality of life using DLQI questionnaire also revealed significant reduction in DLQI scores from baseline in three treatment groups [p value < 0.001, Wilcoxon signed rank test]. Similar to CU-Q2oL scores, no statistically significant difference was noted in DLQI scores at 6 weeks between the groups. This was concordant with the findings of Zuberbier *et al.*[69] who reported significant change in DLQI from baseline in both bilastine and levocetirizine group when compared to placebo and no statistically significant difference existed between the two active treatment groups. While significant reduction in DLQI scores with treatment has been noted with fexofenadine by Thompson *et al.*,[77] Hide *et al.*[66] noted superiority of bilastine when compared with placebo and Johnson *et al.*[78] noted superiority of LCZ when compared with rupatadine.

With regards to the side effect profile of the drugs, most common side effect noted was sedation. Four (16%) patients in levocetirizine group, 4 (12.5%) patients in bilastine group and 4 (14.8%) patients in fexofenadine group had experienced sedation. Other side effects i.e., headache, dry mouth, dry eyes, nausea, vomiting, diarrhoea, constipation, anorexia and hypersensitivity were not recorded in any group. Our findings were concordant with Podder et al. [55] who noted similar sedation with bilastine (12.9%) but are discordant while comparing sedation with levocetirizine (63%). In a study comparing bilastine with levocetirizine and placebo, headache was the most commonly observed side effect (12.1%, 12.1% and 9.2% respectively) followed by sedation (5.8%, 6.7% and 3.3% respectively). However, no statistically significant difference was noted between the three groups while comparing side-effects.[69]

Over the past decades several authors have assessed the efficacy of antihistamines in controlling symptoms of chronic spontaneous urticaria and also attempted to study the laboratory biomarkers of urticaria, in order to provide better symptom control and to identify markers to objectively assess disease severity or treatment response. Our study adds to the growing body of literature on these aspects of chronic spontaneous urticaria. Most studies have been done on European and East Asian ethnicity, while ours has been done on a relatively lesser studied Indian population. Our study attempted to compare the efficacy of a relatively newer antihistamine i.e., bilastine with more frequently used levocetirizine and fexofenadine in controlling symptoms of CSU. Moreover, we observed variation in basophil count to compare response to treatment in all treatment groups thereby adding strength to our observation. Another strength of our study was to note the quality of life of patients of CSU through two standard tools. Evaluation of CU-Q2oL score, an urticaria-specific score, was done along with DLQI to analyse the effect of treatment on quality of life of these patients.

We have identified certain drawbacks in our study including a relatively small sample size, difficulty experienced by patients of different literacy background in recording QoL scores, and recruitment of patients of CSU irrespective of their disease severity.

CONCLUSION

CONCLUSION

We carried out a randomised open labelled study on patients with chronic spontaneous urticaria. A total of 95 patients were recruited in the study out of which 11 patients were lost to follow up. We recorded relevant history, examination findings, weekly urticaria activity score(UAS7), chronic urticaria quality of life questionnaire (CU-Q2oL) and dermatology life quality index (DLQI) scores. Venous blood samples were collected and analysed for basophil counts at baseline. Patients were randomised into three groups with allocation concealment into levocetirizine (5 mg once daily), bilastine (20 mg once daily) or fexofenadine (180 mg once daily) treatment groups. Patients were followed up at 2 weekly intervals for 6 weeks and assessed for response to treatment and treatment related side effects. At each follow up, UAS7 and CU-Q2oL scores were recorded. Patients reporting inadequate control at follow-up visits were subjected to dose escalation to a maximum of four fold. At the end of 6 weeks, UAS7, CU-Q2oL, DLQI scores and basophil counts were repeated. Clinical response and impact on quality of life was assessed in each group and between the groups analysing the change in the above-mentioned parameters. The following key results were obtained:-

- All the three drugs (levocetirizine, bilastine and fexofenadine) caused significant decline in UAS7 score at the end of 6 weeks and the decline was comparable across all treatment groups.
- For better symptom control in inadequately responding patients, up-dosing was required in all the three treatment groups and this escalation was comparable across groups.
- At the end of 6 weeks of treatment, none of the treatment group showed significant change in basophil count when compared from baseline.
- All the treatment groups registered a significant decline in CU-Q2oL scores from baseline and had comparable scores at the end of 6 weeks.
- A significant decline in DLQI was recorded in all the groups at 6 weeks when compared to the baseline. There was no significant difference in DLQI scores among three treatment groups at the end of the study.
- All the three treatment groups were comparable with respect to their side effect profile.

Bilastine has been recently approved for use in CSU, therefore studies comparing this antihistamine with the more frequently used like levocetirizine and fexofenadine are limited. Our study highlighted the similar efficacy of all the drugs in controlling symptoms in

urticaria. The side effect profile was alike in all the three treatment groups. In patients with inadequate response, up-dosing of antihistamines in all the three groups provided additional symptom control without any significant side effect. Although we found no significant change in basophil count after treatment with antihistamines further research is required to accurately ascertain its utility as marker of treatment response in CSU. In our study the three drugs appear comparable in controlling symptoms of urticaria and thereby improving quality of life scores in these patients. In order to find a relatively superior therapeutic agent more studies with larger sample size and additional antihistamines are required.

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BIBLIOGRAPHY

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ANNEXURES

ANNEXURES

ANNEXURE-I

INSTITUTIONAL ETHICS COMMITTEE CERTIFICATE

अखिल भारतीय आयुर्विज्ञान संस्थान, जोधपुर
All India Institute of Medical Sciences, Jodhpur
संस्थागत नैतिकता समिति
Institutional Ethics Committee

No. AIIMS/IEC/2021/3465 **Date: 12/03/2021**

ETHICAL CLEARANCE CERTIFICATE

Certificate Reference Number: **AIIMS/IEC/2021/3300**

Project title: **"Comparison of the efficacy of oral Levocetirizine, Bilastine and Fexofenadine in Chronic Spontaneous Urticaria: An Open-labelled Randomised Controlled Trial"**

Nature of Project:	**Research Project Submitted for Expedited Review**
Submitted as:	**M.D. Dissertation**
Student Name:	**Dr. Shilpi Tyagi**
Guide:	**Dr. Abhishek Bhardwaj**
Co-Guide:	**Dr. Saurabh Singh, Dr. Anil Budania, Dr. Anupama Bains, Dr. Suman Patra & Dr. Abhishek Purohit**

Institutional Ethics Committee after thorough consideration accorded its approval on above project.

The investigator may therefore commence the research from the date of this certificate, using the reference number indicated above.

Please note that the AIIMS IEC must be informed immediately of:

- Any material change in the conditions or undertakings mentioned in the document.
- Any material breaches of ethical undertakings or events that impact upon the ethical conduct of the research.
- In case of any issue related to compensation, the responsibility lies with the Investigator and Co-Investigators.

The Principal Investigator must report to the AIIMS IEC in the prescribed format, where applicable, bi-annually, and at the end of the project, in respect of ethical compliance.

AIIMS IEC retains the right to withdraw or amend this if:

- Any unethical principle or practices are revealed or suspected
- Relevant information has been withheld or misrepresented

AIIMS IEC shall have an access to any information or data at any time during the course or after completion of the project.

Please Note that this approval will be rectified whenever it is possible to hold a meeting in person of the Institutional Ethics Committee. It is possible that the PI may be asked to give more clarifications or the Institutional Ethics Committee may withhold the project. The Institutional Ethics Committee is adopting this procedure due to COVID-19 (Corona Virus) situation. If the Institutional Ethics Committee does not get back to you, this means your project has been cleared by the IEC.

On behalf of Ethics Committee, I wish you success in your research.

Dr. Praveen Sharma
Member Secretary
Member secretary
Institutional Ethics Committee
AIIMS,Jodhpur

Basni Phase-2, Jodhpur, Rajasthan-342005; **Website:** www.aiimsjodhpur.edu.in; **Phone:** 0291-2740741 Extn. 3109
E-mail : ethicscommittee@aiimsjodhpur.edu.in; ethicscommitteeaiimsjdh@gmail.com

ANNEXURE-II

CASE PROFORMA

Comparison of the efficacy of oral Levocetirizine, Bilastine and Fexofenadine in Chronic Spontaneous Urticaria: An Open-labelled Randomised Controlled Trial

Serial No: AIIMS ID:

Patient Name:

Age/ Sex:

Father's name:

Address

1. **Education status:** : Illiterate Primary school Middle school
   High school Intermediate Graduate Professional
2. **Occupation:**

3. **History:**

i. Total duration of illness:
   A. Duration of present episode:
ii. Frequency of wheals: 1 – 3/ week 3 – 5/ week >5/week
iii. Duration of wheals: < 6 hours / > 6 hours to <24 hours / > than 24 hours
iv. Presence of diurnal variation: Yes /No
v. Occurrence in relation to weekends, holidays, travel or menstrual cycle: Yes/No
   If yes, Details_____
vi. Size and colour:
vii. Shape of wheals:
viii. Distribution of wheals: Face / Upper limb / Lower Limb / Trunk
ix. Presence of angioedema: Yes /No
x. Associated subjective symptoms: Itching / Pain / None.
xi. Possible predictive factors: food/ exercise/ weather conditions
   If yes, Details: _____

4. **Past History:**

i. K/C/O thyroid disease-

ii. H/O atopy- Yes /No

iii. Psychiatric comorbidities: - Yes /No

iv. H/O chronic NSAIDs use: Yes /No

5. **Family history** of urticaria or atopy: Yes /No

If yes, Details_____

6. **Personal History:** Addictions: Yes /No

If yes, Details_____

7. **Previous treatment** used: Yes /No

If yes, Details: _____

DRUG NAME	**TREATMENT DETAILS**	**DURATION**	**RESPONSE**

8. **General Examination:**

Pallor – Icterus – Cyanosis – Clubbing –

Lymphadenopathy – Pedal oedema – BMI-

9. **Systemic Examination:**

CVS –

RS –

GIT –

CNS

10. Cutaneous Examination:

Active wheals – Yes / No

Size of lesions - <1cm / 1 - 5 cm/ > 5 cm

Distribution of lesions: Lower limbs/ Upper limbs/ Trunk/ Face

Number: - <20 / 20 – 50 / >50 or large confluent lesions

Morphology –

11. Physical Tests:

Dermographism - Present/ Absent

12. Clinical Assessment:

PARAMETERS / **VISITS**	**TREATMENT GIVEN**	**UAS 7**	**CU-Q2oL**	**DLQI**	**BASOPHIL COUNT**
DAY 0 **DATE:**					
DAY 14 **DATE:**					
DAY 28 **DATE:**					
DAY 42 **DATE:**					

13. Investigations:

	PRE TREATMENT	**POST TREATMENT**
Hb	**g/d L**	**g/d L**
TLC	$x10^3/\mu l$	$x10^3/\mu l$
DLC	N L M E B	N L M E B
Platelet Count	lakhs/ µl	lakhs/ µl
Basophil count	/µl	/µl
ESR	mm in the 1st hour	mm in the 1st hour
LFT		
KFT		
Urine R/M:		
Stool O/P:		
TSH(mIU/L)		

ANNEXURE-III

URTICARIA ACTIVITY SCORE

TABLE 7 The urticaria activity score (UAS7) for assessing disease activity in CSU

Score	Wheals	Pruritus
0	None	None
1	Mild (<20 wheals/24 h)	Mild (present but not annoying or troublesome)
2	Moderate (20-50 wheals/24 h)	Moderate (troublesome but does not interfere with normal daily activity or sleep)
3	Intense (>50 wheals/24 h or large confluent areas of wheals)	Intense (severe pruritus, which is sufficiently troublesome to interfere with normal daily activity or sleep)

For UAS7, the score has to be calculated for the disease activity for each day, with the total score ranging from 0 to 6 .The cumulative score of 1 week forms Urticaria Severity Score 7.

UAS7 score- < or equal to 6 = well controlled,

07 to 15 = mild

16 to 27 = moderate

28 to 42 = severe

Day	Wheals	Pruritus	Total Score
1	0 1 2 3	0 1 2 3	0 1 2 3 4 5 6
2	0 1 2 3	0 1 2 3	0 1 2 3 4 5 6
3	0 1 2 3	0 1 2 3	0 1 2 3 4 5 6
4	0 1 2 3	0 1 2 3	0 1 2 3 4 5 6
5	0 1 2 3	0 1 2 3	0 1 2 3 4 5 6
6	0 1 2 3	0 1 2 3	0 1 2 3 4 5 6
7	0 1 2 3	0 1 2 3	0 1 2 3 4 5 6
		UAS 7	

ANNEXURE-IV

UAS7 RECORDING SHEET

Days	Wheals	Itching	Total score
Day 1	0 1 2 3	0 1 2 3	0 1 2 3 4 5 6
Day 2	0 1 2 3	0 1 2 3	0 1 2 3 4 5 6
Day 3	0 1 2 3	0 1 2 3	0 1 2 3 4 5 6
Day 4	0 1 2 3	0 1 2 3	0 1 2 3 4 5 6
Day 5	0 1 2 3	0 1 2 3	0 1 2 3 4 5 6
Day 6	0 1 2 3	0 1 2 3	0 1 2 3 4 5 6
Day 7	0 1 2 3	0 1 2 3	0 1 2 3 4 5 6
Day 8	0 1 2 3	0 1 2 3	0 1 2 3 4 5 6
Day 9	0 1 2 3	0 1 2 3	0 1 2 3 4 5 6
Day 10	0 1 2 3	0 1 2 3	0 1 2 3 4 5 6
Day 11	0 1 2 3	0 1 2 3	0 1 2 3 4 5 6
Day 12	0 1 2 3	0 1 2 3	0 1 2 3 4 5 6
Day 13	0 1 2 3	0 1 2 3	0 1 2 3 4 5 6
Day 14	0 1 2 3	0 1 2 3	0 1 2 3 4 5 6
Day 15	0 1 2 3	0 1 2 3	0 1 2 3 4 5 6
Day 16	0 1 2 3	0 1 2 3	0 1 2 3 4 5 6
Day 17	0 1 2 3	0 1 2 3	0 1 2 3 4 5 6
Day 18	0 1 2 3	0 1 2 3	0 1 2 3 4 5 6
Day 19	0 1 2 3	0 1 2 3	0 1 2 3 4 5 6
Day 20	0 1 2 3	0 1 2 3	0 1 2 3 4 5 6
Day 21	0 1 2 3	0 1 2 3	0 1 2 3 4 5 6
Day 22	0 1 2 3	0 1 2 3	0 1 2 3 4 5 6
Day 23	0 1 2 3	0 1 2 3	0 1 2 3 4 5 6
Day 24	0 1 2 3	0 1 2 3	0 1 2 3 4 5 6
Day 25	0 1 2 3	0 1 2 3	0 1 2 3 4 5 6
Day 26	0 1 2 3	0 1 2 3	0 1 2 3 4 5 6
Day 27	0 1 2 3	0 1 2 3	0 1 2 3 4 5 6
Day 28	0 1 2 3	0 1 2 3	0 1 2 3 4 5 6
Day 29	0 1 2 3	0 1 2 3	0 1 2 3 4 5 6
Day 30	0 1 2 3	0 1 2 3	0 1 2 3 4 5 6
Day 31	0 1 2 3	0 1 2 3	0 1 2 3 4 5 6
Day 32	0 1 2 3	0 1 2 3	0 1 2 3 4 5 6
Day 33	0 1 2 3	0 1 2 3	0 1 2 3 4 5 6
Day 34	0 1 2 3	0 1 2 3	0 1 2 3 4 5 6
Day 35	0 1 2 3	0 1 2 3	0 1 2 3 4 5 6
Day 36	0 1 2 3	0 1 2 3	0 1 2 3 4 5 6
Day 37	0 1 2 3	0 1 2 3	0 1 2 3 4 5 6
Day 38	0 1 2 3	0 1 2 3	0 1 2 3 4 5 6
Day 39	0 1 2 3	0 1 2 3	0 1 2 3 4 5 6
Day 40	0 1 2 3	0 1 2 3	0 1 2 3 4 5 6
Day 41	0 1 2 3	0 1 2 3	0 1 2 3 4 5 6
Day 42	0 1 2 3	0 1 2 3	0 1 2 3 4 5 6

ANNEXURE-V

CHRONIC URTICARIA- QUALITY OF LIFE QUESTIONNAIRE

Practical problems
Are you affected by itch?
Are you affected by wheals (welts)?
Are you affected by swelling (e.g. of lips or eyes)?
Activities
Urticaria interferes with my regular activities at home or at work
Urticaria interferes with my recreational activities
Does urticaria affect your sleep?
Do you have difficulty falling asleep?
Do you feel tired during the day because of your bad night sleep?
Mood
Does urticaria affect your mood?
Are you feeling irritable because of your symptoms?
Do you feel embarrassed because of your condition?
Are you embarrassed to go into public places?
Do you put limits on your food choices because of urticaria?
Do you have limits on your physical activity because of urticaria?
Are you affected by side effects from your medications?

RESPONSES	KEY
0	Not affected
1	Hardly affected at all
2	Slightly affected
3	Moderately affected
4	Quite a bit affected
5	Very affected
6	Extremely affected

ANNEXURE-VI

DERMATOLOGY LIFE QUALITY INDEX

DERMATOLOGY LIFE QUALITY INDEX (DLQI)

Hospital No:	.	**Date:**	.
Name:	.	**Score:**	.
Address:	.	**Diagnosis:**	.
	.		

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick (✓) one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	☐ ☐	Not relevant ☐
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	☐ ☐ ☐	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐

Please check you have answered EVERY question. Thank you.

ANNEXURE-VII

ALL INDIA INSTITUTE OF MEDICAL SCIENCES, JODHPUR

INFORMED CONSENT FORM

Title of Thesis/Dissertation: **Comparison of the efficacy of oral Levocetirizine, Bilastine and Fexofenadine in Chronic Spontaneous Urticaria: An Open-labelled Randomised Controlled Trial**

Name of PG Student : **Dr. Shilpi Tyagi**

Tel. No. : **7470912896**

Patient/Volunteer Identification No. :_____

I,_____S/o or D/o_____

R/o_____

give my full, free, voluntary consent to be a part of the study **"Comparison of the efficacy of oral Levocetirizine, Bilastine and Fexofenadine in Chronic Spontaneous Urticaria: An Open-labelled Randomised Controlled Trial ",** the procedure and nature of which has been explained to me in my own language to my full satisfaction. I confirm that I have had the opportunity to ask questions.

I understand that my participation is voluntary and I am aware of my right to opt out of the study at any time without giving any reason.

I understand that the information collected about me and any of my medical records may be looked at by responsible individual from _____ (Company Name) or from regulatory authorities. I give permission for these individuals to have access to my records.

Date: _____ _____

Place: _____ Signature/Left thumb impression

(If minor, Parent/Guardian signature)

This to certify that the above consent has been obtained in my presence.

Date: _____ _____

Place: _____ Signature of PG Student

1. Witness 1

_____

Signature

Name: _____

Address: _____

2. Witness 2

_____

Signature

Name: _____

Address: _____

ANNEXURE-VIII

अ खल भारतीय आयु र्वज्ञान संस्थान

जोधपुर, राजस्थान

सू चत सहमति प्रपत्र

थी सस का शीर्षक: क्रॉनिक स्पोनटेनियस आर्टि कयारिया में ओरल लेवोसेटिरिज़िन, बि लस्तीन और फेक्सोफेना डन की प्रभावकारिता की तुलना : एक औपन लेबलङ पेरेल्ल डजाइन राँडो मज़ेड कंटरौलङ अध्धयन

पीजी छात्र का नाम: डॉ. शल्पी त्यागी मोबाइल नंबर: **7470912896**

रोगी / स्वयंसेवी पहचान संख्या _____

मैं, _____ एस / ओयाडी / ओ _____

आर / ओ _____

क्रॉनिक स्पोनटेनियस आर्टि कयारिया में ओरल लेवोसेटिरिज़िन, बि लस्तीन और फेक्सोफेना डन की प्रभावकारिता की तुलना : एक औपन लेबलङ पेरेल्ल डजाइन राँडो मज़ेड कंटरौलङ अध्धयन का एक हिस्सा बनने के लए मेरी पूर्ण, स्वतंत्र, स्वैच्छिक सहमति देता हूँ। जिस प्र क्रयाऔर प्रकृति को मुझे अपनी पूरी संतुष्टि के लए अपनी भाषा में समझाया गया है मैं पुष्टि करता हूं क मुझे प्रश्न पूछने का अवसर मला है।

मैं समझता हूं क मेरी भागीदारी स्वैच्छिक है और मुझे कसी भी कारण दिए बिना कसी भी समय अध्ययन से बाहर निकलने का मेरा अ धकार है।

मैं समझता हूं क मेरे और मेरे मे डकल रिकॉर्ड के बारे में एकत्रित की गई जानकारी को या वनियामक प्रा धकरणों से जिम्मेदार व्यक्ति द्वारा देखा जा सकता है।मैं इन लोगों के लए मेरे रिकॉर्डों तक पहुंच की अनुमति देता हूं।

तारीख : _____ _____

जगह: _____ हस्ताक्षर / बाएं अंगूठे का छाप

(नाबा लग क, माता- पता / अ भभावक के हस्ताक्षर)

यह प्रमा णत करने के लए क मेरी उपस्थिति में उपरोक्त सहमति प्राप्त की गई है

तारीख : _____ _____

जगह: _____ पीजी छात्र के हस्ताक्षर

1. गवाह 1

_____

हस्ताक्षर

नाम: _____

पता: _____

2. गवाह 2

_____

हस्ताक्षर

नाम: _____

पता: _____

ANNEXURE-IX

ALL INDIA INSTITUTE OF MEDICAL SCIENCES, JODHPUR

PATIENT INFORMATION SHEET (PIS)

This document has been given to provide more information about the disease and this research related to Chronic Spontaneous Urticaria.

The current research project is titled: **"Comparison of the efficacy of oral Levocetirizine, Bilastine and Fexofenadine in Chronic Spontaneous Urticaria: An Open-labelled Randomised Controlled Trial**".

Chronic Spontaneous Urticaria is a chronic condition which is characterised by appearance of transient wheals over the skin. These wheals are associated with itching of variable intensity. The aim of the study is to compare the efficacy of different oral medications on disease control and remission. The effect of these drugs on basophil count will also be assessed during the study.

The study will span over a period of 6 weeks, and you (as a participant) will be provided any one of the 3 drugs under study. The drug has to be taken on a daily basis at bedtime and you will be required to record the UAS for each day. You will be expected to take 3 follow-up visits during the course of the study. At each visit, you will be required to score the disease activity and Quality of Life based on UAS7 and CU-Q2oL questionnaire respectively. Any drug induced side effects will also be monitored.

These oral second generation antihistamines may have some side effects like- sedation, drowsiness, head ache, dry mouth, dry eyes, nausea, vomiting, diarrhoea, constipation, anorexia and rarely cardiac arrhythmias and hypersensitivity reactions. All these side-effects are mild, transient and reversible.

The basic goal of this research is to know which of the 3 drugs is better in controlling symptoms of Chronic Spontaneous Urticaria and also their effect on basophil count before and after treatment.

All the information given by you will be kept confidential. You also reserve the right that during this research, you can withdraw the consent & can be out of this research without explaining the reasons.

Principle investigator: Dr.Shilpi Tyagi Contact number: 7470912896

ANNEXURE-X

अ खल भारतीय आयु र्वज्ञान संस्थान

जोधपुर, राजस्थान

रोगी सूचना पत्रक

यह दस्तावेज क्रॉनिक स्पोनटेनियस आर्टि कयारिया रोग के बारे में अ धक जानकारी प्रदान करने के लए दिया गया है और इस से संबं धत यह शोध प्रदान कया गया है।

वर्तमान शोध परियोजना का शीर्षक है: क्रॉनिक स्पोनटेनियस आर्टि कयारिया में ओरल लेवोसेटिरिज़िन, बि लस्तीन और फेक्सोफेना डन की प्रभावकारिता की तुलना : एक औपन लेबलङ पेरेल्ल डजाइन राँडो मज़ेड कंटरौलङ अध्धयन ।

क्रॉनिक स्पोनटेनियस आर्टि कयारिया एक लम्बी चलने वाली बिमारी है , इसमे व्यक्ति के शरीर पर सूजन आती है जो 24 घण्टे के भीतर स्वय ठीक हो जाती है। इस सूजन के साथ खुजली भी होती है। इस अध्ययन का उद्देश्य इस बिमारी में व भन्न दवाईयो की प्रभावकारिता व रोग निवारण क्षमता, की तुलना करना है । इन दवाईयो का बेसौ फल कांउंट पर प्रभाव भी इस परियोजना मे आकलन कया जायेगा ।

यह अध्ययन 6 हफ्तो तक चलेगा व आपको (प्रतिभागी को) इस परियोजना मे रखे गयी दवाओ मे से कोई एक दवा दी जायेगी। वह दवा आपको रोज़ रात को लेनी है और हर दिन का यू ए एस 7 लख कर रखना होगा। परियोजना के दौरान आपको 3 बार आने की अपेक्षा करते है । हर बार रोग की गति व ध व जीवन की गुणवत्ता का आकलन करने के लए सी यू-क्यू 2औ एल प्रश्नावली और डी एल क्यू आई को स्कोर करने के लए कहा जायेगा। दवा के दुष्प्रभाव का भी आकलन कया जायेगा ।

इन दवाओ के कुछ दुष्प्रभाव संभव है - जैसे बेहोशी, तंद्रा, सरदर्द, मुँह व आँखों में सूखापन, मचली, उल्टी, दस्त, कब्ज़, भूख ना लगना और शायद ही कभी हृदय संबंधी अतालता एवम् दवा से अतिसंवेदनशीलता प्रति क्रयाएं हो सकती है । ये सभी दुष्प्रभाव हल्के, क्ष णक व प्रतिवर्ती है ।

इस रीसर्च का मूल लक्ष्य यह जानना है क उपर्युक्त दवाओ मे कौनसी दवा क्रॉनिक स्पोनटेनियस आर्टि कयारिया के लक्षणों को नियंत्रित करने के लए सबसे अ धक प्रभावी है और पूर्व उपचार बेसौ फल कांउंट पर इलाज के बाद कतना प्रभाव पड़ता है ।

आपके द्वारा दी गई सभी जानकारी को गोपनीय रखा जाएगा। आप इस अ धकार को भी सुर क्षत रखते हैं क इस रीसर्च के दौरान, आप बिना कारण बताए सहमति को वापस ले सकते हैं और इस रीसर्च से बाहर हो सकते हैं।

प्रमुख जाँच कर्ता : डॉ. शल्पी त्यागी संपर्क नंबर: 7470912896

ANNEXURE-XI

MASTER CHART WITH IMPORTANT KEY WORDS

S. No.	Variable	Coding
1.	**Age group**	
	18-20 years	**1**
	21-30 years	**2**
	31-40 years	**3**
	41-50 years	**4**
	51-60 years	**5**
	61-65 years	**6**
2.	**Gender**	
	Male	1
	Female	2
3.	**Education**	
	Illiterate	1
	Primary school	2
	Middle school	3
	High school	4
	Intermediate	5
	Graduate	6
	Postgraduate	7
4.	**Occupation**	
	Student	1
	Housewife	2
	Farmer	3
	Businessman/woman	4
	Others (teacher, accountant, tailor, factory worker, policeman, etc)	
5.	**Duration**	
	< 6 months	1
	6-12 months	2
	12-60 months	3

	> 60 months	4
6.	**History of atopy**	
	Present	1
	Absent	2
7.	**Family history of urticarial**	
	Present	1
	Absent	2
8.	**History of thyroid disorder**	
	Present	1
	Absent	2
9.	**Episodes per week**	
	1-3/week	1
	3-5/week	2
	>5/week	3
10.	**Duration of wheals**	
	< 6 hours	1
	6-24 hours	2
11.	**Distribution of wheals**	
	Face	1
	Trunk	2
	Limbs	3
	Face and trunk	4
	Face and limbs	5
	Trunk and limbs	6
	All over the body	7
12.	**Diurnal variation**	
	Day	1
	Night	2
	No variation	3
13.	**History of triggering factors (as per patient)**	
	Present	1
	Absent	2

14.	**History of angioedema**	
	Present	1
	Absent	2
15.	**Active wheals**	
	Present	1
	Absent	2
16.	**Dermographism elicited**	
	Present	1
	Absent	2
17.	Group	
	Levocetirizine	1
	Bilastine	2
	Fexofenadine	3
18.	**Dose escalation**	
	1 time (standard dose)	1
	2 times	2
	3 times	3
	4 times	4
19.	**Change in basophil count**	
	Decrease	1
	No change	2
	Increase	3
20.	**Side effect**	
	Sedation	1
	Others	2
	None	3
21.	**Completed study**	
	Yes	1
	No	2

ANNEXURE-XII

MASTER CHART

S.No	age	age_c	sex	education	occupation_c	duration_months	duration	atopy	family_history	thyroid_disorder	episodes of wheals	duration of weals	Distribution	diurnal	trigger	angioedema	active_weals	dermographism	Group	Dose	UAS7_at_baseline	UAS7_at_2_weeks	UAS7_at_4_weeks	UAS7_at_6_weeks	DLQI_at_baseline	DLQI_at_6_week	CU_QOL_at_baseline	CU_QOL_at_6_weeks	Basophil_ baseline	basephil_6_week	Basophil_difference_c	adverse_effects	completed study
1	41	4	1	5	5	12	3	2	2	2	1	1	6	2	2	2	2	2	1	1	6	3	0	0	2	0	6	0	50	60	3	3	1
2	30	2	1	5	5	36	3	1	2	2	1	1	6	3	2	2	2	2	1	2	6	9	0	0	2	1	13	0	60	70	3	3	1
3	38	3	2	6	2	42	3	2	1	2	1	1	3	2	1	2	2	1	1	1	12	2	0	0	2	0	25	0	20	20	2	3	1
4	40	3	1	4	5	3	1	2	2	2	1	1	7	3	2	2	1	1	1	1	12	0	0	1	4	0	16	0	0	0	2	3	1
5	24	2	1	1	5	9	2	2	2	2	1	1	6	1	2	2	2	2	1	1	12	0	2	2	6	1	17	2	20	20	2	1	1
6	20	1	1																														2
7	20	1	2	6	1	3	1	2	2	2	1	1	7	2	2	1	2	2	1	2	13	16	4	4	4	1	24	1	50	30	1	3	1
8	32	3	2																														2
9	41	4	2	3	2	48	3	1	2	2	`	1	6	3	2	2	1	2	1	2	14	7	4	4	5	0	17	2	0	60	3	3	1
10	43	4	1	6	5	6	1	2	1	2	3	2	7	1	2	2	1	1	1	3	15	12	10	4	5	2	19	6	30	30	2	1	1
11	18	1	1	5	1	42	3	2	2	2	2	2	7	2	2	1	2	2	1	4	16	17	8	10	12	2	61	8	0	0	2	3	1
12	50	4	2	6	2	12	2	2	2	2	1	1	5	2	2	2	2	1	1	2	18	0	0	0	3	0	18	0	40	50	3	3	1
13	19	1	1																														2
14	20	1	2	6	1	6	1	2	2	2	2	2	7	1	1	1	2	2	1	1	20	2	0	0	4	0	21	0	20	30	3	3	1
15	33	3	2	4	2	2	1	2	2	2	3	1	7	1	2	1	2	1	1	1	20	0	0	0	7	0	21	0	10	10	2	3	1
16	39	3	2	6	5	12	1	2	2	2	1	1	7	2	1	1	2	2	1	1	21	2	0	2	5	1	47	0	20	40	3	3	1
17	32	3	2	6	2	3	1	2	2	2	3	1	7	3	2	2	2	1	1	2	26	11	6	6	7	1	42	3	30	20	1	3	1
18	26	2	2	6	2	120	4	2	2	2	3	1	7	3	2	2	2	2	1	2	28	16	0	0	8	0	19	0	50	50	2	3	1
19	55	5	2	6	2	12	3	2	2	2	3	1	6	2	2	2	2	2	1	1	35	0	0	2	6	0	20	0	0	0	2	3	1
20	18	1	2	6	1	96	4	1	2	2	2	2	6	3	2	2	1	2	1	2	24	14	0	0	8	0	27	0	0	0	2	3	1
21	19	1	1	5	1	3	1	2	2	2	3	1	7	2	2	1	2	2	1	1	42	0	0	0	10	0	33	2	0	0	2	3	1
22	22	2	1	5	5	12	3	2	2	2	3	1	7	2	2	2	2	2	1	1	42	2	0	4	5	0	27	0	20	30	3	3	1
23	23	2	2																														2
24	30	2	2	6	4	12	2	2	2	2	3	1	7	2	1	1	1	1	1	1	28	2	0	0	17	5	52	4	20	40	3	1	1
25	30	2	1	6	4	2	1	2	2	2	1	1	7	1	2	2	2	1	1	2	16	3	3	2	5	1	26	1	0	20	3	3	1
26	45	4	2	1	2	24	3	2	2	2	3	2	7	2	2	1	2	2	1	3	20	14	5	7	8	1	23	7	40	30	1	3	1
27	22	2	1	3	4	36	3	2	2	2	3	1	7	2	2	2	2	2	1	2	28	20	6	4	6	3	27	4	0	10	3	1	1
28	51	5	1	4	5	24	3	2	2	2	3	2	3	1	2	2	1	2	1	2	14	10	0	0	4	0	14	0	20	20	2	3	1
29	45	4	2	1	2	3.5	1	2	2	2	3	1	7	2	2	1	2	2	1	4	42	30	22	18	8	2	42	4	30	20	1	3	1
30	58	5	1	6	5	24	3	2	2	2	3	2	7	2	1	1	1	2	2	4	34	23	16	**6**	5	0	28	3	0	0	2	3	1
31	37	3	2	1	2	60	4	2	2	2	3	2	7	2	2	2	2	2	2	3	42	11	0	26	4	0	54	3	10	60	3	3	1
32	36	3	1	7	5	48	3	2	1	2	1	1	7	2	2	1	1	1	2	3	28	22	16	14	11	7	44	29	20	30	3	1	1
33	24	2	1	6	5	12	3	2	2	2	2	1	6	1	2	2	2	1	2	1	20	0	0	0	11	0	11	0	40	20	1	3	1
34	28	2	1																														2
35	26	2	2	3	2	8	2	2	2	2	3	1	6	2	2	1	1	2	2	1	21	0	0	0	1	0	17	0	0	0	2	3	1
36	46	4	2	1	2	42	3	2	2	1	2	1	7	2	1	1	2	2	2	2	15	5	7	5	3	1	23	2	30	20	1	3	1
37	48	4	2	6	5	240	4	2	2	2	3	1	7	2	2	1	2	2	2	3	39	4	13	**6**	6	0	28	0	30	20	1	3	1
38	40	3	2	1	2	24	3	2	2	1	3	1	7	1	2	1	1	1	2	1	42	2	0	0	6	0	38	0	0	0	2	3	1
39	22	2	2	6	1	1.5	1	2	1	2	2	2	7	2	2	2	2	2	2	1	15	14	9	6	3	1	7	2	10	10	2	3	1
40	25	2	2	6	5	12	3	2	2	2	3	2	6	2	1	2	1	1	2	3	26	28	9	5	16	1	61	1	10	10	2	3	1
41	20	1	2	6	1	24	3	2	2	2	3	1	7	3	2	2	1	1	2	1	34	1	0	0	8	0	18	0	20	20	2	3	1
42	39	3	2	1	2	18	3	2	2	2	1	2	7	2	2	1	1	2	2	2	21	12	0	0	6	1	23	4	10	10	2	1	1
43	20	1	1	6	1	48	3	2	2	2	1	1	6	2	2	2	2	2	2	1	15	0	0	0	6	0	22	0	70	20	1	3	1
44	24	2	2	6	1	180	4	2	2	2	1	1	7	1	2	2	1	2	2	3	35	18	7	3	4	0	10	0	20	20	2	3	1
45	25	2	1																														2
46	20	1	1	6	4	4	1	2	2	2	2	1	7	2	2	1	2	2	2	1	16	5	0	0	5	0	11	0	0	20	3	3	1
47	23	2	2	4	4	12	3	2	2	2	3	1	6	3	2	2	1	2	2	1	42	0	0	0	4	0	24	1	30	0	1	3	1
48	34	3	1	6	4	3	1	2	2	2	2	1	7	3	2	2	2	2	2	1	14	4	1	0	2	0	12	0	10	40	3	3	1
49	26	2	1	6	4	6	1	2	2	2	1	1	6	1	2	2	1	2	2	1	10	6	0	0	4	0	23	0	40	50	3	3	1
50	47	4	2	1	2	6	1	2	2	2	1	1	6	2	2	1	2	2	2	1	4	1	0	0	3	0	25	0	20	20	2	3	1
51	45	4	2	1	2	24	3	2	2	2	3	2	7	2	2	1	1	2	2	3	20	20	14	10	8	2	23	7	40	30	1	3	1
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53	24	2	1	6	4	24	3	2	2	2	1	1	6	2	2	2	2	2	2	1	12	7	0	0	3	0	10	0	10	10	2	3	1
54	20	1	2	6	1	2	1	1	2	2	2	1	7	1	2	2	2	2	2	1	8	0	0	0	3	0	18	0	50	70	3	3	1
55	26	2	1	6	1	2.5	1	2	2	2	3	1	6	2	2	1	2	2	2	2	42	12	0	0	6	0	16	0	20	40	3	3	1
56	26	2	2	6	5	6	1	2	2	2	1	1	7	3	2	1	2	2	2	1	15	0	0	0	3	0	11	0	20	20	2	3	1
57	36	3	2																														2
58	42	4	2	4	2	3	1	2	2	2	3	1	6	3	2	1	2	2	2	1	42	7	6	**6**	9	0	21	4	40	30	1	3	1
59	44	4	2	1	3	6	1	2	2	2	3	1	7	3	2	2	1	1	2	1	42	4	0	0	10	0	36	0	20	20	2	3	1
60	35	3	1	4	4	36	3	1	2	2	3	1	3	3	1	2	2	2	2	1	21	0	0	0	3	0	14	0	20	10	1	3	1
61	21	2	2	3	3	120	4	1	2	2	3	1	6	3	1	2	2	2	2	3	35	35	14	21	6	4	20	16	50	40	1	1	1
62	43	4	1	3	5	12	3	2	2	2	1	1	6	2	2	2	1	2	2	1	12	0	0	0	3	0	10	0	20	20	2	3	1
63	26	2	2	6	5	16	4	2	2	2	3	2	7	2	2	1	1	2	2	2	21	10	0	3	1	0	9	2	30	40	3	1	1
64	21	2	2	4	5	3	1	1	2	2	1	1	6	3	1	2	1	1	2	1	28	4	0	3	9	1	35	2	20	10	1	3	1
65	27	2	2	1	2	4	1	2	2	2	3	1	6	2	2	2	1	1	3	2	25	14	0	0	9	1	42	0	0	0	2	3	1
66	28	2	2	3	2	12	3	2	2	2	3	2	7	1	2	1	2	2	3	2	28	10	4	0	6	0	44	1	50	60	3	3	1
67	27	2	1	6	5	4	1	2	2	2	1	1	7	2	2	1	1	1	3	2	15	11	4	0	9	0	68	0	20	10	1	3	1
68	24	2	2																														2
69	29	2	2	3	2	48	3	2	2	2	3	1	6	2	1	2	1	1	3	2	42	32	6	7	10	0	39	0	60	40	1	3	1
70	25	2	2	5	2	36	3	1	2	2	1	1	7	2	2	2	2	1	3	1	12	6	3	4	8	0	43	4	30	30	2	1	1
71	28	2	1	6	1	18	3	2	2	1	3	2	6	1	2	2	2	2	3	2	42	0	10	0	14	0	57	0	10	20	3	3	1
72	21	2	1	6	1	2	1	2	1	2	1	1	7	2	2	2	2	2	3	1	2	0	0	0	5	1	33	3	50	50	2	3	1
73	30	2	2	6	2	18	3	2	2	2	1	2	7	2	1	1	2	2	3	1	4	0	0	0	8	0	31	0	30	40	3	3	1
74	65	6	2																														2
75	45	4	1	4	3	12	2	2	2	2	1	2	7	2	2	2	2	2	3	3	15	10	10	0	4	0	17	0	10	40	3	3	1
76	42	4	1	2	3	60	4	2	2	2	1	2	6	3	2	2	2	2	3	2	12	8	6	6	6	1	16	5	10	10	2	3	1
77	20	1	2	5	1	24	3	1	1	2	3	1	7	3	2	1	2	2	3	2	36	9	2	1	12	0	62	2	30	10	1	3	1
78	24	2	1	5	4	6	1	2	2	2	3	1	6	2	2	2	1	2	3	2	20	9	2	2	6	3	29	4	20	10	1	1	1
79	48	4	2	3	2	3	1	2	2	2	1	1	7	2	2	2	2	2	3	1	12	0	0	0	5	0	14	0	80	70	1	3	1
80	42	4	2	1	2	60	4	2	2	2	3	1	7	3	2	1	2	2	3	2	15	10	2	0	13	4	48	14	70	0	1	3	1
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82	18	1	1	6	1	48	3	1	2	2	2	1	6	2	2	1	2	2	3	1	20	6	6	7	10	0	25	0	10	10	2	3	1
83	57	5	1																														2
84	24	2	1	4	4	36	3	2	2	2	2	1	6	3	2	2	2	2	3	1	20	0	0	0	5	0	16	0	20	10	1	3	1
85	21	2	1	5	1	6	1	2	2	2	1	1	6	3	2	2	2	2	3	3	23	23	36	12	5	2	18	6	10	40	3	3	1
86	32	3	1	6	5	2	1	2	2	2	2	1	7	1	2	1	2	2	3	2	28	6	24	21	4	3	18	10	10	10	2	3	1
87	28	2	2	6	1	30	3	2	2	2	2	1	6	3	2	2	2	1	3	2	16	11	0	0	7	2	18	3	20	30	3	1	1
88	18	1	2																														2
89	20	1	2	5	1	1.5	1	2	1	2	1	1	6	2	2	2	2	2	3	1	9	0	0	0	4	0	17	0	10	20	3	3	1
90	20	1	2	5	5	18	3	1	2	1	1	1	7	2	2	2	2	2	3	1	12	2	0	2	12	1	46	2	30	50	3	3	1
91	46	4	2	1	2	4	1	2	2	2	1	1	7	2	2	2	2	2	3	1	18	0	0	0	5	0	26	0	40	30	1	3	1
92	37	3	1	6	5	6	1	2	2	2	2	1	7	1	1	2	1	1	3	1	16	5	0	4	7	0	39	0	60	10	1	3	1
93	31	3	2	6	2	180	4	2	2	2	3	1	7	1	1	1	1	2	3	1	28	0	0	0	7	0	27	1	30	20	1	1	1
94	21	2	1	6	1	1.5	1	2	2	2	3	1	6	2	2	1	2	2	3	2	28	16	0	0	16	0	49	0	10	10	2	3	1
95	21	2	2	6	1	12	3	2	2	2	3	1	6	3	2	2	2	1	3	1	42	2	0	0	10	0	39	0	30	0	1	3	1