A PROSPECTIVE RANDOMIZED OPEN LABEL COMPARATIVE STUDY OF MONTELUKAST AND RANITIDINE AS AN ADD ON THERAPY TO CETIRIZINE IN CHRONIC URTICARIA

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M.D. (PHARMACOLOGY)

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CHENGALPATTU MEDICAL COLLEGE

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CERTIFICATE

This is to certify that this dissertation entitled, **"A PROSPECTIVE, RANDOMIZED, OPEN LABEL, COMPARATIVE STUDY OF MONTELUKAST AND RANITIDINE AS AN ADD ON THERAPY TO CETIRIZINE IN CHRONIC URTICARIA"** submitted by **Dr.S.Sweetlin**, in partial fulfillment for the award of the degree of M.D.(Pharmacology) by The Tamilnadu Dr.M.G.R.Medical University, Chennai is a bonafide record of the research work done by her, under the guidance of **Dr.K.Baskaran, M.D.,** Professor and Head, Department of Pharmacology, Chengalpattu Medical College during the academic year 2014-17 in the Department of Pharmacology, Chengalpattu Medical College ,Chengalpattu- 603001.

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I solemnly declare that the dissertation entitled **"A PROSPECTIVE, RANDOMIZED, OPEN LABEL, COMPARATIVE STUDY OF MONTELUKAST AND RANITIDINE AS AN ADD ON THERAPY TO CETIRIZINE IN CHRONIC URTICARIA"** is done by me at Chengalpattu Medical College and hospital, Chengalpattu during the period of 2015-2016 under the guidance and supervision of **Dr.K.Baskaran, M.D.,** Professor and Head, Department of Pharmacology, Chengalpattu Medical College. This dissertation is submitted to The Tamilnadu Dr.M.G.R.Medical University, Chennai towards the partial fulfilment of the requirements for the award of **M.D. DEGREE IN PHARMACOLOGY.**

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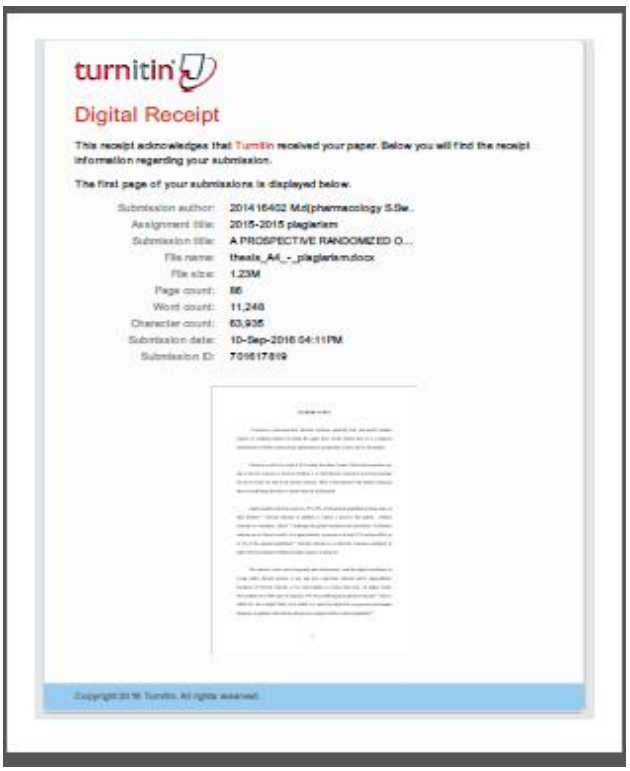

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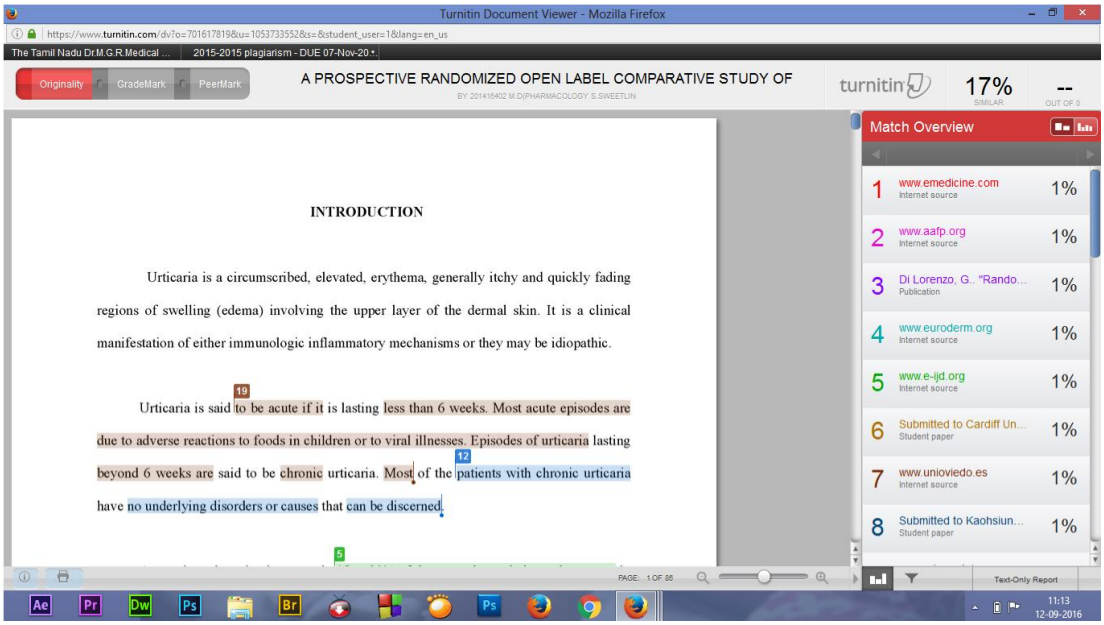

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INTRODUCTION

Urticaria is a circumscribed, elevated, erythema, generally itchy and quickly fading regions of swelling (edema) involving the upper layer of the dermal skin. It is a clinical manifestation of either immunologic inflammatory mechanisms or they may be idiopathic.

Urticaria is said to be acute if it is lasting less than 6 weeks. Most acute episodes are due to adverse reactions to foods in children or to viral illnesses. Episodes of urticaria lasting beyond 6 weeks are said to be chronic urticaria. Most of the patients with chronic urticaria have no underlying disorders or causes that can be discerned.

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ABBREVIATIONS

RST	-	Radio Allergo Sorbent test
UAS_7	-	Urticaria Activity Score
EAACI/GA^2LEN/ EDF/WAO	-	European Academy of Allergy and Clinical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum/World Allergy Organisation
IgE	-	Immunoglobhlin E
CysLT	-	Cysteinyl Leukotriene
VLA	-	Very Late Activation
C5a	-	Complement 5a
NK	-	Natural Killer
TNF	-	Tumor Necrosis Factor
ECP	-	Eosinophil Cationic Protein
IL3	-	Interleukin – 3
VCAM 1	-	Vascular Cell Adhesion Molecule
ICAM 1	-	Intercellular Adhesion Molecule
MHC	-	Major Histocompatability Complex
PG D_2	-	Prostaglandin D_2
ASST	-	Autologous Serum Skin Test
ELISA	-	Enzyme Linked Immunosorbent Assay
CBC	-	Complete Blood Count
ESR	-	Erythrocyte Sedimentation Rate
ANA	-	Anti Nuclear Antibodies
GM-CSF	-	Granulocyte Monocyte-Colony Stimulating Factor
NF-B	-	Nuclear Factor-B
PUVA	-	Psoralen Ultra Violet A
PAF	-	Platelet Activating Factor
IVIG	-	IntraVenous Immunoglobulin
JTFPP	-	Joint Task Force on Practice Parameters
BSACI	-	British Society for Allergy and Clinical Immunology
ANOVA	-	Analysis Of Variance
LTRA	-	Leukotriene Receptor Antagonist

ABSTRACT

Title: A PROSPECTIVE RANDOMIZED OPEN LABEL COMPARATIVE STUDY OF MONTELUKAST AND RANITIDINE AS AN ADD ON THERAPY TO CETIRIZINE IN CHRONIC URTICARIA

Background:

Chronic urticaria is a highly distressing disease affecting a person's life quality. In most cases, monotherapy fails. Hence, combination of antihistamines with montelukast, H_2blockers,ciclosporin,dapsone,omalizumab are used with varying results.

Aim:

To assess the efficacy and safety of the combination therapy of Montelukast and Cetirizine with Ranitidine and Cetirizine in chronic urticaria patients.

Methodology:

Hundred patients were recruited,randomized and medications were given to group A (Cetirizine + Montelukast) and group B (Cetirizine + Ranitidine). Complete history, clinical examination and laboratory investigations were done at the beginning of the study. Patients were educated to keep a daily record of Urticaria Activity Score (UAS7) over seven consecutive days in a descriptive chart. Review of patient's UAS7 record and clinical examination were done at every weekend. Sum of score at the end of every week for 4 weeks were calculated and recorded.

Results:

The mean weekly UAS in group A were 18.67, 10.07, 4.65, 1.74 and in group B were 27.77, 19.38, 13.68 and 8.04 respectively.Significant difference in symptom reduction between group A and group B was found to be favouring group A. The mean total UAS in group A was 35.13, group B is 68.87 ($p< 0.001$).

Conclusion:

Montelukast seems to be a promising medication as add-on therapy to cetirizine both in the aspect of efficacy and safety in patients affected by chronic urticaria.

Keywords: chronic urticaria, cetirizine, montelukast, ranitidine

INTRODUCTION

Urticaria is a circumscribed, elevated, erythema, generally itchy and quickly fading regions of swelling (edema) involving the upper layer of the dermal skin. It is a clinical manifestation of either immunologic inflammatory mechanisms or they may be idiopathic.

Urticaria is said to be acute if it is lasting less than 6 weeks. Most acute episodes are due to adverse reactions to foods in children or to viral illnesses. Episodes of urticaria lasting beyond 6 weeks are said to be chronic urticaria. Most of the patients with chronic urticaria have no underlying disorders or causes that can be discerned.

Approximately urticaria occurs in 15 to 20% of the general population at least once in their lifetime[(1)]. Chronic urticaria in addition to reduce a person's life quality, affects outcome at workplace, school [(2)].Although the global incidence and prevalence of chronic urticaria are not known exactly, it is approximately occurring in at least 0.1% and possibly up to 3% of the general population[(3)]. Chronic urticaria is a relatively common condition in India. But exact disease burden in Indian scenario is unknown.

The urticaria occurs most frequently after adolescence, with the highest incidence in young adults, though persons of any age may experience urticaria and/or angioedema. Incidence of Chronic urticaria is two times higher in women than men. An Indian study showed that out of 500 cases of urticaria, 37% were suffering from physical urticaria[(4)]. HLA-DRB1*04,

HLA-DQB1*0302, HLA-DRB1*15, and HLA-DQB1*06 are present with higher frequency in patients with chronic urticaria as compared with a control population[5].

Diagnostic studies should be based on findings elicited by the history and physical examination. There is little role for routine prick skin testing or the radio allergo sorbent test (RAST) in the diagnosis of specific IgE-mediated antigen sensitivity in chronic urticaria/angioedema.

In chronic urticaria, disease activity assessment in scientific researches as well as in routine clinical practice must be done using Urticaria Activity Score(UAS7), which is a unified and easy scoring method which was suggested in the EAACI/GA2LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria and has been validated. In this score, the signs and symptoms of chronic urticaria assessment is done by the patient themselves thus improving the scores' validity[2].

The UAS is based on the assessment of key symptoms of urticaria which are wheals and pruritus. It is suitable for the evaluation of disease activity by urticaria patients and their treating physicians. Furthermore, this scoring system has been widely used in trials and should thus be maintained for future comparison. As urticaria symptoms change frequently in intensity, the overall disease activity is best measured by advising patients to document 24-h self-evaluation scores once daily for several days.

Urticaria is known to be due to a number of pathophysiological mechanisms. Urticaria may develop after IgE- or IgE receptor–mediated reactions; due to abnormalities of the complement system and other plasma effector systems; after direct mast cell degranulation; or in association with activation of the arachidonic acid metabolic pathways of the cells.

The major effector cell in most forms of urticaria is mast cells, though other cell types may be involved. Urticaria is due to a local increase in permeability of capillaries and venules. Vascular permeability in skin is produced by the interaction of both H_1 and H_2 histamine receptors. Activation of H_1 receptors in the skin induces itching, flare, erythema, whealing and contraction of smooth muscle in respiratory and gastro-intestinal tract. Stimulation of H_2 receptors leads to erythema and whealing in the skin and increased gastric acid secretion.

There are studies showing the combination of chlorpheniramine (H_1 antagonist) and cimetidine (H_2 antagonist) to be more successful in inhibiting a histamine skin reaction when compared with an H_1 antagonist alone, and it is recommended for the treatment of chronic idiopathic urticaria[6]. Other studies with cetirizine and ranitidine, diphenhydramine and ranitidine, terfenadine and ranitidine showed similar results[7,8]. It has been told that the H_1 antagonist-H_2 antagonist combination inhibits the release of allergic mediators, whether IgE dependent or otherwise[9–11].

But antihistamines are only partially effective in inhibiting wheal formation in some chronic urticaria patients, hence it is very probable that other mediators apart from histamine may play a role in wheal formation in chronic urticaria[12,13]. Injected leukotriene D_4 is more potent than histamine in causing a wheal and flare[14].

Montelukast blocks the action of leukotriene D_4 on the cysteinyl leukotriene receptor $CysLT_1$ in the lungs. Leukotriene receptor antagonists like montelukast have been tried in chronic urticaria with variable results. Since leukotriene-mediated urtication is not blocked by other agents, leukotriene antagonists can be helpful[15].

Rationale of this study:

There are many clinical trials and isolated observations with multiple treatments either as monotherapy or in combination. It is mentioned in the guideline for urticaria -2013 revision and update by the joint initiative of the Dermatology Section of the European Academy of Allergy and Clinical Immunology (EAACI), the EU-funded network of excellence, the Global Allergy and Asthma European Network (GA2LEN), the European Dermatology Forum (EDF), and the World Allergy Organization(WAO) that areas of further research in urticaria with controlled multicenter trials regarding the possible effect of add-on therapy of anti-H_2, montelukast, sulfone, methotrexate, azathioprine[2].

Most of the trials have assessed the efficacy of add on therapy of montelukast with other anti histamines like hydroxyzine, desloratidine, fexofenadine, ebastine etc, but with cetirizine, trials are less that too in Indian population. Similarly trials on role of add on therapy of H_2 blocker in chronic urticaria among Indian population is very less.

Based on above information regarding need for further research in this field, in our study we aim to compare the efficacy and safety of combination therapy of Cetirizine and Montelukast versus Cetirizine and Ranitidine in chronic urticaria.

REVIEW OF LITERATURE

Urticaria is a disease manifested by the appearance of fleeting type of wheals which are itchy central swelling with erythema surrounding it. Urticaria is derived from the Latin word *urtica*, "nettle" meaning "to burn". The occurrence of urticaria and angioedema is influenced by various factors like age, sex, race, geographic areas, occupation and particular season of the year.

HISTORY

Although urticaria was recognised as an entity, its cause was a great mystery to the physicians of earlier times. In the 10th century B.C, urticaria was named as 'Feng Yin Zheng' meaning "wind type concealed rash" in China[16]. The disease has had numerous names in various cultures. In the B.C 4th century, Hippocrates noticed the similarities in the symptoms of urticaria and lesions produced after contact with a herb plant which irritates the skin or bites from insects. He named the disease 'cnidosis' which means nettle rash[17].

In the literature of Indian Ayurveda, the phrase '*sheeta pitta'* was used, pitta refers to one among the 3 humors which is mandatory for maintainence of the body health in humans[18].

Many terms like 'elevation' in Arabic meaning-'essera', 'Uredo' were in usage; *urere is a* Latin word with the meaning - to burn, contributed to the 'urticatio'. The disease was called by Frank in 1972 by its presently accepted term called 'urticaria'[18].

CLASSIFICATION

Urticaria is a heterogeneous group of disorders which may be classified based on duration of disease and their clinical features.

Clinically urticaria is classified as follows:

1. Ordinary urticaria
   - Acute
   - Episodic
   - Chronic
2. Physical and cholinergic urticarias
3. Contact urticaria
4. Urticarial vasculitis
5. Angioedema without weals
6. Other syndromes resembling urticaria or angioedema, or with urticaria as a component.

Acute urticaria :

Type of urticaria, in which if the wheals are completely resolving within six weeks duration, it is called as acute urticaria[19]. If a person is being exposed to an allergen, in case of acute urticaria, the lesions usually develop within a few minutes. Though in a period of six weeks, the hives disappear, it takes several weeks for the outbreak to resolve.

The trigger which is causing this acute urticaria is unknown in nearly half of the cases. In the other half, the contributing factors commonly encountered are foods, bee or wasp stings, skin contact with plants and their products,some fragrances etc., One more common cause of acute urticaria is

acute viral exanthems. The triggering factors less commonly attributed to the development of acute urticaria are temperature, pressure, exercise, friction, sunlight and extremes.

Chronic urticaria :

Chronic urticaria which is also named as ordinary urticaria[20] is characterised by the presence of wheals that are evanescent in nature and are persisting for more than six weeks period[19].

In severe forms of chronic urticaria, the signs and symptoms may even last longer than 20 years. In study conducted, it was found that in 50% of the patients, chronic urticaria was found to be persisting for nearly one year or more. The same survey revealed that about 20% of patients were suffering from this illness for a period longer than 20 years.

Angioedema occurs concurrently with chronic urticaria in about 87% of patients and is also frequent in autoimmune urticaria. Urticaria can be highly distressing and can cause personal, social and occupational disability[21–24]. Autoimmunity may be a main contributing factor for an accountable number of cases as evidenced by latest trials, though lot of chronic urticaria cases are still categorised to be idiopathic. [25 ,26]. Acute urticaria and chronic urticaria are very difficult to be differentiated visually alone. The male: female ratio of chronic urticaria is 2:1 and hence the disease is more common among females in the general population [25].

INCIDENCE AND PREVALENCE:

Urticaria is a very common disorder, with a point prevalence of 0.1% in one survey; in familial research showing 0.27-2.1%; allergy clinics visits shows 10 % [26-30]. It is estimated that the cumulative lifetime prevalence of chronic urticaria is varying widely from 0.05% - 23.6% in the general population, but a more realistic range seems to be between 1-5% [3, 26].

With global incidence of urticaria estimated to be between 0.1% - 0.3%, it has been found that among five people, one will have urticaria once during their life period.

AETIOLOGY:

In most cases, though IgE mediated release of histamine is said to be the cause of urticaria, non-IgE, nonimmunologic stimulation of mast cell is found to contribute as well. Autoimmune substances like IgE antibodies are seen in serum of some patients with chronic urticaria , yet the significance of their presence is still unclear. Only in 10 to 20 percent of chronic cases a particular trigger is found [31].

Commonly encountered triggers are allergens, insect envenomation, food pseudoallergens (i.e., foods and food additives which has histamine or which may trigger the releasing of histamine directly, like preservatives, tomatoes, strawberries and some coloring agents), infections, insect envenomation and medication [32-34].

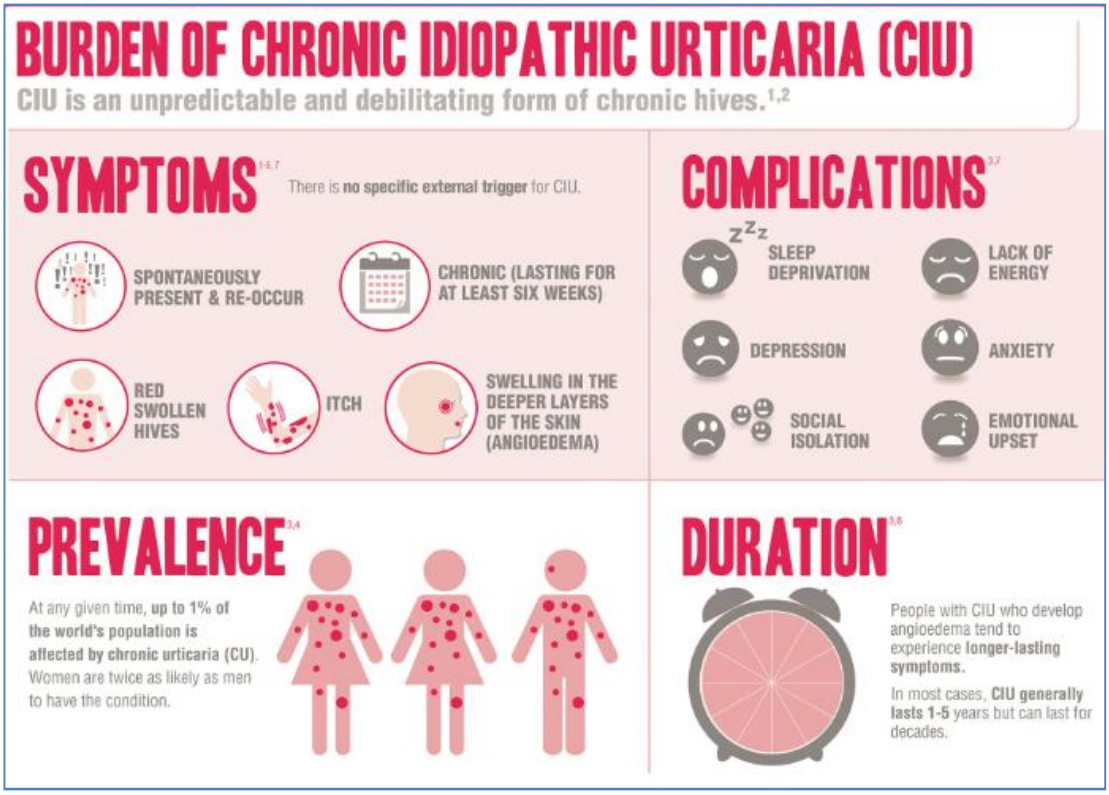


FIGURE 1 : BURDERN OF CHRONIC URTICARIA

Allergic reactions to drugs may manifest as urticaria, commonly seen with antibiotics. Some medications like nonsteroidal anti-inflammatory drugs, aspirin, vancomycin, opiates, radiocontrast dye and muscle relaxants produce urticarial reactions through direct mast cell degranulation(35).

Various Causes of Urticaria are as follows:

1. **Immunoglobulin E mediated**

   Aeroallergens

   Food allergens

   Contact allergen

   Drugs (allergic reaction)

   Insect venom

   Parasitic infections

2. Nonimmunoglobulin E mediated

Autoimmune disease

Infections (bacterial, fungal, viral)

Cryoglobulinemia

Vasculitis

Lymphoma

3. Nonimmunologically mediated

Core body temperature elevation

Pseudoallergens in food

Light

Medications (direct mast cell degranulation)

Physical stimuli (cold, local heat, pressure, vibration)

Water

TABLE 1: BASED ON PATIENT HISTORY AND PHYSICAL EXAMINATION- URTICARIA ETIOLOGIES [36]

CLINICAL CLUE	POSSIBLE ETIOLOGY
Abdominal pain, dizziness, shortness of breath, stridor, tachycardia	Anaphylaxis
Dermatographism	Physical urticaria
Food ingestion immediately before symptoms	Food allergy
Medication use or change	Medication allergy or direct mast cell degranulation
Physical stimuli	Physical urticaria
Smaller wheals (1 to 2 mm), burning or itching, brought on by heat or exercise	Cholinergic urticaria
Travel	Parasitic or other infection
Upper respiratory tract infection or urinary tract infection symptoms	Infection
Weight gain, cold intolerance	Hypothyroidism
Weight loss (unintentional	Lymphoma
Wheals lasting more than 24 hours, burning, residual hyperpigmentation	Urticarial vasculitis

PATHOPHYSIOLOGY:

Lot of theories [37] regarding the pathogenesis of urticaria were described.

1. **Humoral theory:**

This theory relates urticaria to fluids present in the body i.e, 'humors'

2. **Meterologic theory**:

In this theory, it was said that urticaria manifests as a result of the constellation of the stars. This theory was proposed in 1823.

3. **Menstrual theory**:

This theory proposed in 1864 believes the relationship of endogenous hormones to urticaria.

The Mast cell's discovery by the scientist Paul Ehrlich in the year 1879 is a major contribution for our present knowledge regarding the urticarial pathogenesis.

The pathological picture chararcteristic to urticaria is the presence of superficial oedema in the dermis. In urticaria, the wheals' age and its cause is a one which decides the wide spectrum of pathological changes that is seen in the affected cells.

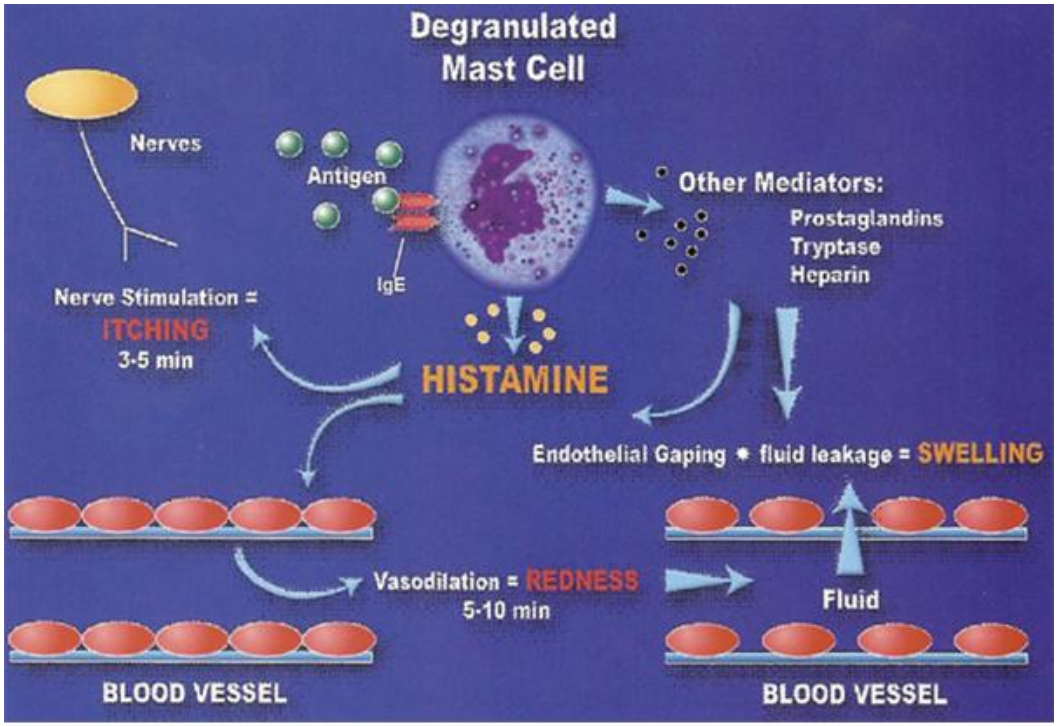


FIGURE 2: **CASCADE OF EVENTS IN URTICARIA**

In case of acute urticaria, oedema and dilated venules are seen in the interstitium, also the endothelial cells are swollen but inflammatory cells are few in number. Besides the edema in the dermis, in chronic urticaria numerous lymphocytes, neutrophils, monocytes, eosinophils are found to be infiltrating the perivascular region as well as the interstium of the dermis.

The role of the mast cell in vivo in urticaria and angioedema was studied by analysis of the alterations in the morphology of mast cells, in tissues or biologic fluids by identification and quantitation of products of the mast cell. Dermal blood perfusion has been studied using Scanning laser Doppler imaging and the presence of biochemical mediators involved in the disease process and their actions are evaluated by dermal microdialysis.

A recent hypothesis is that the alterations in vasopermeability is due to the release of mast cell products along with the expression of adhesion molecules on the surface of the endothelial cells followed by the rolling and attachment of leukocytes in the blood which enter the microenvironment in the skin[38].

Mast cells present in the skin adhere to fibronectin and laminin by means of Very Late Activation (VLA) ß 1 integrins, similarly to vitronectin by the avß 3 integrin. Histamine is released in response to C5a, morphine and codeine only by the cutaneous mast cells and not by the mast cells in other sites.

Number of mast cells present in the areas of lesions and nonlesional skin of chronic urticaria patients are comparable and they are not in fact different from the numbers in the skin controls of unaffected individuals, yet in very small number of studies increased number of mast cells were observed in the lesional regions of the skin of chronic urticaria patients.

In chronic urticaria, sparse or dense number of inflammatory cells are found to be infiltrating the dermis which include more of CD4 than CD8 T lymphocytes, eosinophils, neutrophils and basophils [39] whereas B lymphocytes or natural killer (NK) cells are not present. Neutrophils are the predominant cell type in certain tissues. Increased number of TNF-α and IL-3 are expressed on the endothelial cells as well as perivascular cells of the upper portion of the dermis in patients with acute and chronic idiopathic urticaria.

Major basic protein and eosinophil cationic protein (ECP) are substances that are derived from the eosinophil granule [40]. These are found surrounding the blood vessels as well as dispersed in the dermal lesions of acute urticaria, chronic idiopathic urticaria and delayed-pressure urticaria, cholinergic urticaria and solar urticaria. In case of chronic idiopathic urticaria, freely distributed eosinophilic granules are found to be increased in the dermis with wheals of more than 24 hour duration as compared to wheals that lasts less than 24 hour.

The secreted form of eosinophil cationic protein (ECP) and eosinophil-derived neurotoxin were seen on cells in larger amounts in biopsy specimens from patients with chronic urticaria without autoantibodies as compared with those with autoantibodies. P-selectin, E-selectin, ICAM-1 and VCAM-1 have been identified on the vascular endothelium of patients having chronic urticaria with dermographism.

Up regulation in the Major Histocompatability Complex (MHC) class II antigen on the endothelial cells of chronic urticaria patients is also noted; the peripheral blood lymphocytes have increased CD40 ligand expression and higher Bcl-2 expression; these observations suggest an augmentation of autoimmune phenomena.

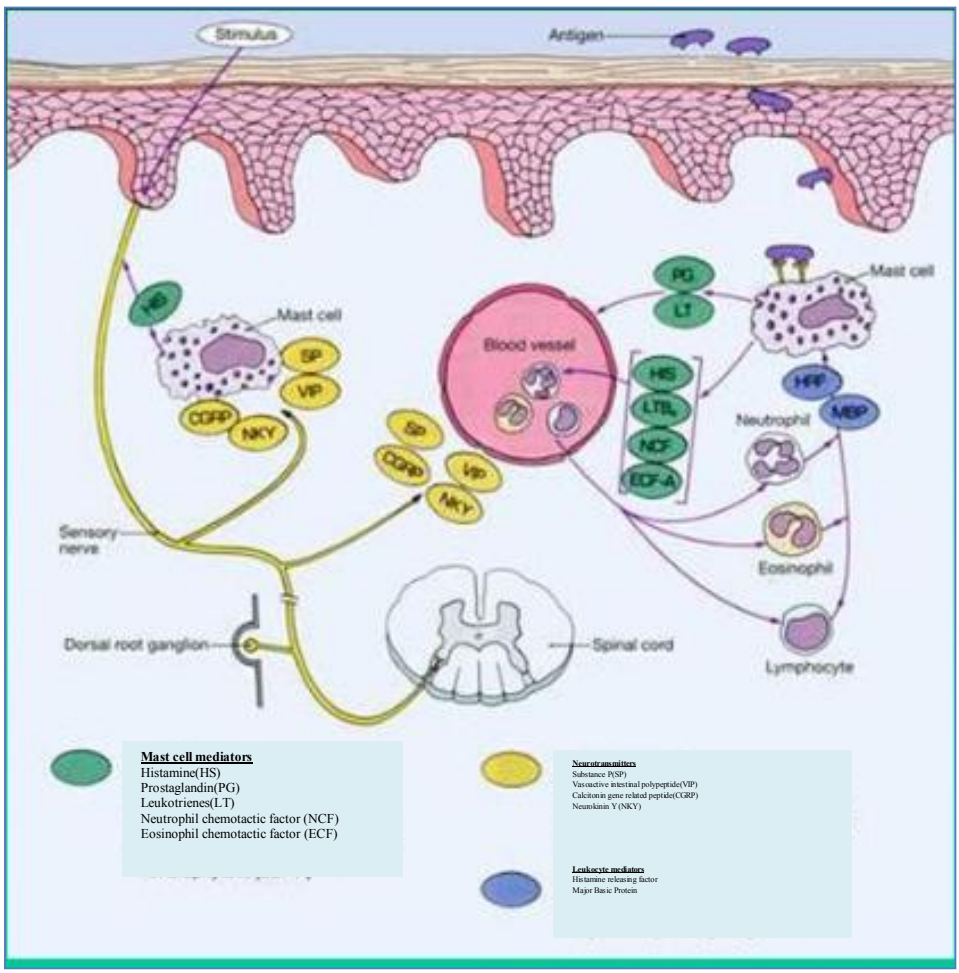


FIGURE 3: PATHOGENESIS OF CHRONIC URTICARIA

Though the major mediator is histamine, newly made mediators that are synthesised from the arachidonic acid are PGD_2 as well as leukotrienes like C4, D4 and E4[25,41,42].Leukotriene C4, in producing a wheal-and-flare, is 1000 times highly potent when compared to histamine ,so it may also be considered as an additional mediator of urticaria [43]. From the arachidonic acid, a component of the phospholipid bilayer of cell membrane, leukotrienes are synthesized by the inflammatory cells like mast cells/basophils, neutrophils, eosinophils, monocytes/macrophages and lymphocytes. Montelukast is known to block the effect of leukotriene D4 on the cysteinyl leukotriene receptor

CysLT1 present in the lungs. In the treatment of chronic urticaria, leukotriene receptor antagonists like montelukast were used with variable results.

It is an already known fact that the blood vessels present in the skin have H_1 as well as H_2 receptors. Nearly 85% of the histamine receptors seen in the human skin are H_1 receptors, while the remaining 15% are H_2 receptors. Stimulation of both H1 and H2 receptors is found to be responsible for the formation of wheal and erythema - though H2 stimulation has less effect over the warmth and itching [7].

Hence, the addition of a H_2 blocker to a H_1 receptor antagonist accelerates the inhibition produced by H_1 -receptor antagonist in reducing the histamine-induced wheal-and-flare reaction once histamine-receptor blockade has been increased. Over all combining H_2 receptor blockers with an H_1 receptor antagonist provides some additional benefit.

Inspite of our insight about urticaria's pathogenesis, this disease still leaves many patients disabled even with the availability of various treatment facilities.

CLINICAL FEATURES

The clinical features of urticaria includes recurrent wheals which are normally pink-to-red pruritic raised oedematous plaques having pale centers. The transient wheals in many categories of urticaria are lasting for not more than 24 hours [25]. The size of the wheals in diameter differs between a few millimeter to several centimeter. However, the various sized wheals can

confluence forming a larger plaque. The shape of the wheals varies from round to irregular. Reagarding distribution, wheals can appear anywhere over the skin, which includes the palms,soles and the scalp. The urticarial wheals are generally paler compared to the reddish skin that surrounds it which is due to the post-capillary venules being compressed by the dermal edema. The lesions are almost pruritic and unique because the itch is not relieved by scratching, but by rubbing. A very commonly encountered consequence of this itch is purpura when compared to excoriations[26]. The intensity of the itch is at the peak during evenings as well as night- time , occasionally 'burning' or 'pricking' in nature.

Signs and symptoms

Lesions of urticaria are of transient type, where individual wheals typically persisting for a period of less than 24 hours. Pruritus is the most common symptom associated with chronic urticaria.

Typical lesions can be manifested as follows:

- Primary lesions appear as erythematous and edematous plaques or papules with a pale center (wheal) surrounded by erythema (flare)
- Lesions seems to be pale or red (depending on background skin color)
- Lesions can be either generalized or localized.
- Shape of the lesions can be round, annular, oval, arcuate, serpiginous.
- No post inflammatory pigmentary changes or scaling is seen following the disappearance of the lesions.

DIAGNOSTIC TOOLS

Researchers are insisting that eliciting a elabortive history from the patient is generally enough to make a diagnosis of urticaria of chronic nature [25, 44-47]. In situations where there is a need for laboratory tests, an Erythrocyte Sedimentation Rate (ESR) and total blood count along with differential count can be done.

In case if a trigger factor is not found, few physicians suggest screening to rule out *H. pylori* infection. The Autologous Serum Skin Test (ASST) is found to be useful in differentiating chronic urticaria of autoimmune etiology from chronic idiopathic urticaria to some extent [25 ,44]. Tests for thyroid antibodies and thyroid function are needed in situations that favour diagnosing thyroid disease [48]. In case of patients with features of urticarial vasculitis, a skin biopsy should be done for confirming. Challenge test is done if physical urticaria in a patient is being evaluated. Patients with angioedema, without urticaria should be screened for deficiency of C1 inhibitor by measuring their C4 levels. If the measured C4 level is found to be less, then measurement of C1 inhibitor levels should be done [25,44,48].

Due to the aggressive nature of disease and their greater resistance to treatment, chronic urticaria of immune etiology should be clinically differentiated from chronic idiopathic urticaria. It was shown by Sabroe *et al*. that patients who are positive for auto antibodies presented with more wheals and wider distribution of lesions, greater itch scores, more systemic symptoms and lower IgE levels in serum than patients who are negative for

auto antibodies [49]. These patients, in addition, are having more chance of being benefited by immunosuppressive agents rather than conventional therapies. Due to the absence of a reliable laboratory tests, diagnosing autoimmune urticaria is a difficult one for the clinicians. A reduction in basophils (basopenia) is found to be a common finding of chronic urticaria which may be used for screening autoimmune type chronic urticaria[50,51]. But, no method is found to be feasible and accurate in determining basophil count from the peripheral blood of the patient. Direct tests for antibodies are not reliable unfortunately; immunobinding techniques and ELISA also gives us disappointing results[26].

ASST is currently the most contributing test in the evaluation of chronic urticaria. In this test, through the uninvolved skin of the forearm, serum from the patient themselves is drawn during a flare episode and intradermal injection of the same is given. At the same time, injection of saline as well as histamine controls is given. In cases where the result is said to be positive, diameter of the wheal is 1.5 mm greater at the serum-injected site compared to the saline-injected site. This test is having a sensitivity of about 65–81% and specificity of 71–78% [41]. *In vitro* testing, the gold standard test that demonstrates histamine release by the mast cells as well as basophils present in the dermal layer of healthy donors will confirm any positive wheal reaction if obtained [41]. The ASST in addition is used to monitor the disease course . Hence, an exacerbation of symptoms gives a positive test whereas a negative result is consistent with symptom remission [52].

Generally, once a patient has no auto antibodies against the mast cells, chronic urticaria diagnosis is established. In such patients, chance of finding the etiology of urticaria is almost rare.

Laboratory investigations:

The following Laboratory studies are used in the diagnosis of chronic urticaria:

- Complete Blood Count (CBC) with differential:

In patients with parasitic infections, especially in developing countries and also in patients experiencing any drug reaction, the eosinophil count may be elevated.

- Examination of the stool for ova and parasites:

Should be considered in patients with gastrointestinal tract symptoms and positive travel history or an elevated eosinophil count.

- Erythrocyte Sedimentation Rate (ESR):

May be elevated in persons with urticarial vasculitis .

- Antinuclear antibody (ANA) titers:

Indicated when urticarial vasculitis is suspected.

- Hepatitis B and C titers:

Hepatitis B and C may be associated with cryoglobulinemia, which is associated with some forms of cold induced urticaria and urticarial vasculitis.

- Serum cryoglobulin and Complement assays:

  - Cryoglobulinemia is associated with some forms of cold induced urticaria.

  - C3 (associated with pulmonary involvement in a subset of patients with urticarial vasculitis), C4 (sometimes low in hereditary angioedema), and C1 esterase inhibitor (associated with hereditary angioedema) functional assays may be performed.

- Thyroid function testing and antithyroid microsomal and peroxidase antibody titers:

Patients with urticaria unresponsive to antihistamines or steroids may have elevated titers [53]; the plasma thyrotropin level helps screen for thyroid dysfunction.

- Chronic Urticaria (CU) Index:

Patients with a chronic form of urticaria who have a positive functional test result for autoantibody to the Fc receptor of immunoglobulin E (IgE), that is, anti-FceR—likely have an autoimmune basis for their disease .

A biopsy of the skin is necessary for diagnosing urticarial vasculitis or a neutrophil-predominant pattern of urticaria which may not resolve with antihistamines. It is also indicated in patients whose lesions are associated with petechiae or purpura, and also for patients with systemic symptoms like fever, arthralgia or arthritis.

In different studies, there seems to be considerable variations in the frequency of causes underlying the disease. This reflects the regional differences in the world, for example, various traditional diets as well as different in the prevalence of infections. Hence, it is necessary to remember that not every possible causative factor is to be investigated in all patients and the initial step in diagnosis is a thorough history. Intensive, costly general screening programs to evaualate the causes of urticaria are strongly advised against.

The EAACI/GA2LEN/EDF/WAO guideline recommend for only limited extended diagnostic assessment in chronic urticaria based on patient history (strong recommendation/clinical consensus). It also recommends that the Urticaria Activity Score(UAS7) should be used in routine clinical practice to find the disease severity in patients with chronic urticaria[54].Comparing UAS7 scores at different visiting helps to monitor disease activity over a period of time. Weekly Urticaria Activity Score (UAS7) denotes the average Urticaria Activity Score for 7 days.

In this scoring, patient will be asked to circle the score that corresponds to the number of wheals/pruritis severity over 7 consecutive days. Patient's responses will help the doctor assess how active their chronic urticaria is.

The UAS7 for assessing disease activity in chronic urticaria is as follows:

TABLE 2: UAS 7 SCORE [54-56]

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

Sum of score: 0–6 for each day is summarized over one week (maximum 42)

Since the disease manifestations tend to change over from time to time, current recommendation is documentation of symptomatology using UAS for a consecutive period of days. Scoring method which is easy to apply and validated is UAS7, in which one time a day evaluation for number of hives and itch intensity/severity is done during 7 consecutive days. This UAS7 is supposed to be finished by every patient between doctor visits followed by assessment done by doctor as well as patient.

Pruritus' intensity as well as the counting of wheals will be scored seperately from 0 to 3 one time a day with greater scores implying severe disease symptoms. Pruritus and wheal scores on summation provides daily scoring (zero to six). Daily scoring is again summed for that entire week days

to obtain a weekly UAS (UAS7) which ranges between zero and maximum of forty two [54,56].

This UAS7 scorings can be graded based on severity explaining 'chronic urticaria health states', which provides a good knowledge of patient's disease impact as well as therapy response [57]. Zero UAS7 implies patient's pruritus and wheals free state.

TABLE 3: UAS 7 GRADING

UAS7	GRADING
≤ 6	well-controlled
7–15	mild
16–27	moderate
28–42	severe disease

This grading have been suggested. But, clear cut delineation between mild, moderate or severe urticaria is not yet validated.

Yet this scoring was used in omalizumab's clinical trials at Phase III for patients with resistant chronic spontaneous urticaria, where UAS7 score ≥ 16 was kept as an inclusion criteria, because such patients were assumed to have moderate-to-severe chronic urticaria.

Demerits in UAS7

1. In patients with inducible urticarias, it is not applicable.
2. Angioedema cannot be assessed.
3. This provides a prospective assessment alone regarding the symptom process (patients' compliance being important).

DIFERENTIAL DIAGNOSIS[58]

1. Atopic dermatitis
2. Contact sensitivity
3. Cutaneous mastocytosis (urticarial pigmentosa)
4. Systemic mastocytosis

PREVENTION

Identification of offending agents and avoiding it if possible remains the main stay of prevention modality.

TREATMENT

The mainstay in the treatment of urticaria is avoiding triggers along with pharmacological agents. Therapy may be categorised as first line, second line and third line of mananagement.

I. First line management

First line of treatment consists of educating the patient about non therapeutic measures along with a course of H_1 antihistaminic agents whenever there is persisting symptoms [25]. Non therapeutic measures are avoiding exacerbating factors like extreme heat, alcohol, stress etc., [44]. Avoiding medications like NSAIDs, aspirin and ACE inhibitors are also advised [25, 44]. Anti-itching creams with cooling effect with 1% to 2% menthol suspended in aqueous media or calamine cream will be useful [44, 48]. Most important thing is to inform the patients regarding the disease pattern, in verbal

as well as in written form. Particularly, they have to be informed regarding the benign form of the disease, inability to cure, and the difficulty of finding a causative factor most often [44].

Ia. H_1 Antihistamines

H_1 Antihistamines interact with H_1 receptors as inverse agonists. Activation of these H_1 receptor stimulates GPCRs which further acts on transcription factor NF-B as well as inositol triphosphate and diacylglycerol, that in turn blocks synthesis of lot of inflammation mediators like GM-CSF, P-selectin, ICAM-1, VCAM-1, IL-1ß, IL-6, iNO synthase and TNF-alpha [59]. H_1 receptor antagonists are able to inhibit histamine release by blocking the mast cell action on its target cells. Inhibition of hiastaminic receptor reduces allergen induced accumulation of eosinophils.

The antihistamines' efficacy in relieving itching, reducing the count of wheals is nicely documented, though all patients will not respond. At tertiary care clinics, among patients who are treated with antihistamines, only about 40% had complete cure of disease[25]. Few patients show decrease in severity of itchiness, reduction in the count and duration of hives [25]. At the same time, we must be careful to not assume therapeutic failure, when the urticaria does not resolve with one particular antihistamine; multiple antihistamines may be given as in most cases, outcome is usually based on individual patients. H_1 antihistaminics seems to be more effective when they are prescribed daily, than giving it as 'as and when required basis' [25, 44].

Classic/Ist generation antihistamines acting on H_1 receptors are 'hydroxyzine, cyproheptadine, diphenhydramine, and chlorpheniramine'. Due to the side effects like sedation, anticholinergic symptoms, first-generation H_1 receptor antihistaminics are not commonly prescribed as a single drug. However, particularly in patients with sleep disturbances due to urticaria, antihistaminics serves as a valuable add on therapy [25, 44]. Many trust in the reduction of adverse events which slowly wanes among patients having severe urticaria when antihistaminics are taken for a prolonged time; yet this information is not supported by any trials.

Over the last 15 years, many 2nd-generation antihistamines acting on H_1 receptors were discovered whose efficacy is similar to Ist generation antihistaminics yet with lesser side effects. These are 'cetirizine, loratadine, levocetirizine, desloratadine, fexofenadine, mizolastine, ebastine'. Lacking marked CNS and anticholinergic adverse effects are the merits of these 2nd-generation antihistaminics. Though antihistamines are often used in the treatment of allergic conditions at a higher dose than actually advised by the manufacturer to achieve more anti-inflammatory as well as anti-allergic actions, no supportive evidence exists for this [60].

In a latest trial with fexofenadine, formed from terfenadine, it was found that 180 mg once daily dosing was effective as well as tolerated well by those affected by chronic urticaria [61]. Nelson *et al*. concluded in his study of 'dose finding' that fexofenadine 60mg two times a day was found to possess slightly lower efficacy compared to 120mg or 240mg dosage [62]. Fexofenadine,

due to its peculiar lipophobic nature, it is not crossing the BBB and hence prescription of upto 360mg once daily will not cause sleepiness [26].

Desloratadine being loratadine's metabolite has more histamine antagonistic as well as antiinflammatory property compared to loratadine [63]. Mizolastine, must be cautiously used by those having cytochrome P450 CYP) inhibitors like cyclosporine, cimetidine, and nifedipine due to the adverse effect of cardiac arrhythmias especially QT prolongation [25].

Similarly, hydroxyzine's active product cetirizine with same pharmacological action yet lesser sedative effects [64]. Levocetirizine is the l-enantiomer derived from cetirizine which is highly efficacious than its parent compound. It provides faster improvement from symptoms in those suffering from 'chronic urticaria' [65]. Studies that tested the actions of cetirizine and levocetirizine, two 2nd -generation H_1 antihistaminics, have shown these two medications possessing well known antiinflammatory property like prevention of PAF-based adherence of eosinophil to the vascular endothelium, chemotaxis of eosinophil and migration across cells of the endothelium of dermis [66]. In addition, Cetirizine causes downregulation of NF-B synthesis [66].

Ib. H_2 Receptor Antagonists

Patients presenting with symptoms of 'chronic urticaria', adding H_2 receptor antihistamines to H_1 receptor antihistamines have been shown to have beneficial effect [25, 67, 68]. This is because 15% of histamine receptors in the blood vessels of the skin belong to H_2 type [67].

However, using H_2- receptor antagonists as a monotherapy is not recommended, since they are having only lesser action against pruritus. Some H_2 blockers are 'cimetidine, ranitidine, and famotidine' [25]. To conclude, studies which supports the action of H_2 blockers as add on therapy in chronic urticaria are less and much research is needed.

II. Second line management

In cases where the symptoms of urticaria persist with antihistaminics alone, consideration of 2nd line of management is needed, that includes both non-pharmacologic and pharmacologic measures.

IIa. Non-Pharmacologic Therapy :

Inconclusive results were obtained from treatment with phototherapy using Ultra violet lamp / photochemotherapy which uses PUVA with psoralen, although few studies demonstrates PUVA to be more efficacious in treating urticarias of physical origin, yet not that of chronic origin [69]. Results from trials with relaxation treament were too found to be non-conclusive [44].

IIb. Pharmacologic Therapy:

Various groups of drugs are found to be helpful in 2nd -line management with varying results, which includes leukotriene receptor antagonists, antidepressants, calcium channel antagonists, corticosteroids, levothyroxine sodium supplements, etc.,

Leukotriene- Receptor Antagonists

The Leukotrienes being a very effective mediator in the inflammatory process having established effects in eliciting a 'wheal and flare' reaction in persons of good health as well as in 'chronic urticaria' patients [43]. LRAs like zafirlukast, zileuton and montelukast are found to possess higher efficacy as compared to placebo in clinical trials [70, 71]. Also LRAs like montelukast are shown to have useful role by reducing the symptoms of 'chronic urticaria' in those population not responding to monotherapy with antihistaminics [68,72, 73].

Evidences are there to support that in a subgroup of chronic urticaria affected patients showing exacerbation on exposure to NSAIDs may be prevented by leukotriene receptor antagonists [74]. Yet another study concluded that montelukast as an add on therapy to desloratadine was superior in reducing the symptoms of chronic urticaria rather than using desloratadine alone in patients with chronic urticaria [75]. Bagenstose *et al*. too reported that adding zafirlukast to existing treatment with cetirizine has shown greater effectiveness than cetirizine used alone in treating chronic urticaria patients positive to ASST, but it was not so among patients negative for ASST [76].

In spite of the promising results issued by these studies, treating urticaria patients with leukotriene receptor antagonists and their efficacy in improvement of life's quality remains controversial because, beneficial effect is not found in all trials. An example to this negative result is a randomised, placebo controlled, double blinded crossover trial with 52 patients affected by

chronic urticaria. Here, treatment with 20 mg of zafirlukast two times a day alone gave no significant usefulness against placebo [77].

Antidepressants

Doxepin, a tricyclic antidepressant is having potent antagonistic activity at H_1 and H_2 receptor [25, 48] with better efficacy as well as less sedativeness compared to antihistaminics, especially in managing chronic urticaria with diphenhydramine [78]. In contrast, Goldsobel *et al*. has shown doxepin to have sedation as a bigger demerit compared to that seen with hydroxyzine/diphenhydramine [79]. Hence its usefulness in the treatment of urticaria is limited. Due to their sedative effect, this antidepressant acts good when it is given during night. In addition, since CYP enzymes are involved in the doxepin's metabolism, it is to be cautiously used,or else avoided for patients ingesting other medications which are metabolized by this enzyme like cyclosporine, erythromycin and cimetidine. There are evidences to prove Doxepin to be particularly helpful in chronic urticaria affected patients with comorbid depression [48]. Doxepin's dose range for treating depression is between 25- 150 mg daily, yet for chronic urticaria treatment it ranges between 10 and 30 mg daily.

One more antidepressant is Mirtazapine which shows strong antagonistic action upon H_1 receptors, hence showing antipruritic property. Mirtazapine at a dosage of 30mg daily, some patients with physical urticaria as well as pressure urticaria seems to respond well [80].

Corticosteroids

At times, whenever the patient requires faster as well as complete disease control, short course of steroids may be given systemically in case of severe urticaria. Although efficacy of corticosteroids is high enough, long-term treatment cannot be recommended due to their property of development of tolerance besides their various side effects like gastric ulcer, osteoporosis, raise in blood sugar and blood pressure etc., In cases where long term steroid treatment is unavoidable, advisable thing is to take minimal dose that is effective along with addition of a immunosuppressive agent with steroid sparing effect [25, 48, 44, 68, 81].

Zuberbier *et al.* gives option for a short period of systemic corticosteroids as 3rd -line treatment (maximum 10 days) in chronic urticaria or as a choice in acute aggravation of symptoms [54]. Well designed randomized controlled clinical trials regarding role of corticosteroids in chronic urticaria are lacking.

Nifedipine

When used as monotherapy or as an add on therapy with antihistamines, Nifedipine is found as an efficacious therapy in decreasing pruritus as well as wheals seen in urticaria patients with chronic course[82]. However, many researchers have shown that the outcome of nifedipine is not encouraging in urticaria clinically [44]. The mechanism proposed behind the clinical effect of nifedipine is the change in the entry of calcium through the mast cells present

in the skin. It has been reported that in patients having co-morbidity of hypertension, nifedipine can be tried as an optional treatment modality, especially when a patient is already on an Angiotensin Converting Enzyme inhibitor or other multiple antihypertensive regimen with an ACE inhibitor where an another antihypertensive has to be added [25, 44].

III. Third-line Therapy

Immunomodulatory agents like cyclosporine, cyclophosphamide, tacrolimus, methotrexate, intravenous immunoglobulins, mycophenolate mofetil are the 3rd line of treatment options for urticaria patients who are unresponsive to first- and second-line of therapy. Most cases that needed 3rd line of treatment are found to possess autoimmune urticaria. Alternative options of 3rd line treatment which offers some benefits are colchicine, plasmapheresis, hydroxychloroquine, tranexamic acid, dapsone, terbutaline, warfarin and sulfasalazine, [25, 44, 48, 83].

IIIa. Immunomodulatory Agents

It was shown in various studies that cyclosporine is having a beneficial role in the treatment of chronic urticaria patients refractory to treatment[26,84,85]. Nearly 2/3 of chronic urticaria patients failing to improve with antihistamines, are showing better results with 3–5 mg/kg/day of Cyclosporine [48]. Greaves in his trial reported that among the patients he treated, more than 75 percent had shown excellent results with the treatment of cyclosporine [26]. Once the drug

was withdrawn, 1/3 of them remained in remission, mild relapse seen in another one-third and remaining one-third relapsed to pre-treatment status.

Eight out of nineteen patients in a randomized double-blind trial having worsened chronic urticaria shown improvement from cyclosporine treatment versus none among those received placebo[85]. Following cyclosporine treatment, a statistical significance in the reduction of ASST reaction to histamine releasing action of serum was found. Similar results were reported in a double blinded trial by Di Gioacchino *et al* [84] among forty patients who had chronic urticaria with positive ASST and treated by cyclosporine.

It is advisable to continue H_1 antihistaminics during the treatment of cyclosporine, with appropriate monitoring of renal function and blood pressure. To continue cyclosporine as prolonged treatment modality is impossible due to their deleterious side effects like nephrotoxicity, raise in blood pressure and chances of resurgence of symptoms once treatment is withdrawn [25, 48, 68].

Although effectiveness of alternative immunomodulatory drugs (methotrexate, tacrolimus, cyclophosphamide) are highly restricted[48,68], Stanaland has shown excellent results in a recent literature by using tacrolimus at a dose of 20-µg/mL /day for managing urticaria patients who are steroid dependent[86]. Treatment with intravenously administered cyclophosphamide to a patient who was suffering from steroid dependent urticaria has demonstrated 100 percent remission in a case report [87].

There are reports of successful treatment with Methotrexate in two chronic urticaria patients who were negative for ASST and also were non-responders to standard treatment [68, 88]. In a trial by Shahar *et al*. nine patients suffering from chronic urticaria had significant improvement in symptoms after treated with mycophenolate mofetil over twelve weeks [89]. Everyone of them quit prednisone; also serious side effects were not reported.

The efficacy of IV immunoglobulin used for treating severe resistant chronic urticaria of immune nature seems to be good [25, 48, 68]. Though its mode of action is not known, it is believed that anti idiotypic antibodies are present in IV immunoglobulin which may fight against endogenously synthesised IgG to combine with H_1 receptors, blocking release of histamine or otherwise improves clearing of IgG that is produced endogenously [90].

In a trial, O'Donnell *et al*., witnessed that out of 10 cases who had worse chronic autoimmune urticaria, nine were clinically improved as well as a reduction in ASST reaction following larger-dose of IV immunoglobulin for 5 days [91]. Three patients had prolonged period of remissions of 3 years. There is a report which shown complete remission in less than forty eight hours following larger-dose infusion with IV immunoglobulin [90]. Other trials have not found significant beneficial effect [92].

In spite of ASST being negative for about of six months, the patient suffered from recurrence again after seventh month of IV immunoglobulin infusion. Cost and potential morbidity remain as an obstacle in the usage of

IV immunoglobulin. Randomised trials are yet to be carried out for evaluating its usage in urticaria [25, 48, 44, 68].

IIIb. Plasmapheresis

It has been kown that Plasmapheresis is giving promising results in treating worse chronic autoimmune cases. A case series report, has documented that 6 out of 8 cases who had worse non-responding chronic autoimmune urticaria were relieved off their symptoms after plasmapheresis [93].

However, this modalility of treatment cannot be trusted for long term or as monotherapy due to its cost, early relapse of urticaria and potential morbidity. In the prevention of auto antibodies that release histamine from getting accumulated, Plasmapheresis as a monotherapy is insufficient and hence researches are needed to evaluate their use along with immunosuppressive agents [25, 48, 44, 68].

IIIc. Anti-IgE therapy

Anti-IgE antibody, Omalizumab seems to be the most specific and promising therapy for chronic urticaria in the future [94-97]. A typical dose of 150mg every $2^{nd}/4^{th}$ week or 300mg/month for 4–6 doses appears to have lasting efficacy for nearly 15 months ,particularly providing valuable upgradation in one's quality of life [96-98].

The important downside with this therapy is

1. High cost – 1 to 2 subcutaneous injections/month at US $10,000/year and

2. Its yet unknown side effects regarding the parasitic infectious disease burden with its use in India or Asia [99-101].

Here is the summary of pharmacotherapy **guideline algorithms** suggested/adopted by various organisations:

EAACI/GA2LEN/ EDF/WAO	IJTFPP	BSACI
First line : modern second generation antihistamines. **Second line:** Increase 2nd generation antihistamine dosage upto 4 fold. **Third line:** add Omalizumab or CiclosporinA or montelukast. Short period (upto 10 days) of corticosteroids may be used for exacerbations as needed.	**Step1:** second generation antihistamines **Step2:** one or more of the following: dose advancement of 2nd generation antihistamine, add another 2nd generation antihistamine,or add first generation antihistamine at bed time. **Step 3:** dose advancement of potant antihistamine(eg.hydroxy zine or doxepin) as tolerated **Step 4:** add alternative agent, Omalizumab or cyclosporine, other anti-inflammatory agents, immunosuppressants, or biologics.	**Step 1:** second generation antihistamines **Step2:** increase 2nd generation antihistamine dosage up to fourfold or add a 2nd antihistamine **Step 3:** consider an anti-leukotriene agent **Step 4:** go for an immunomodulator(eg. Omalizumab,cyclospo rine) A short course of corticosteroids may be appropriate in severe episodes at any stage.

JTFPP- Joint Task Force on Practice Parameters.

BSACI- British Society for Allergy and Clinical Immunology.

OBJECTIVES

Primary objective:

To compare the efficacy of the combination therapy of Montelukast and Cetirizine with Ranitidine and Cetirizine in patients with chronic urticaria.

Secondary objective:

To assess the safety of the combination therapy of Montelukast and Cetirizine with Ranitidine and Cetirizine in patients with chronic urticaria.

METHODOLOGY

Study Design :

A prospective, randomized, open label, comparative study

Study population:

All patients who are attending the Dermatology outpatient department in Chengalpattu Medical College/ Hospital with history & clinical features of chronic urticaria.

Period of study:

March 2015 to March 2016 (12 months)

Duration of the study:

6 weeks (4 weeks therapy +2 weeks follow-up)

Study centre:

Department of Dermatology,
Chengalpattu Medical College/ Hospital.

Sample size:

100 patients (Group A-50, Group B-50)

SELECTION CRITERIA

Inclusion criteria:

- Chronic urticaria patients not responding to two weeks of treatment with cetirizine 10mg.
- age: 18- 60 years.
- Patients with diabetes, hypertension and other illness that doesn't influence the disease pattern will also be included.
- Patients who are willing to give informed consent.

Exclusion criteria:

- Urticaria of less than 6 weeks duration.
- age: <18yrs & >60yrs.
- pregnant and lactating women.
- chronic urticaria patients who were treated with steroids & other immuno suppressants.
- patients with any focal sepsis.
- drug induced urticaria.
- associated with other skin disorders like eczema,etc.,
- Patients with chronic bronchial asthma who are taking steroids /montelukast.
- Patients with cholestatic jaundice.

STUDY PROCEDURE:

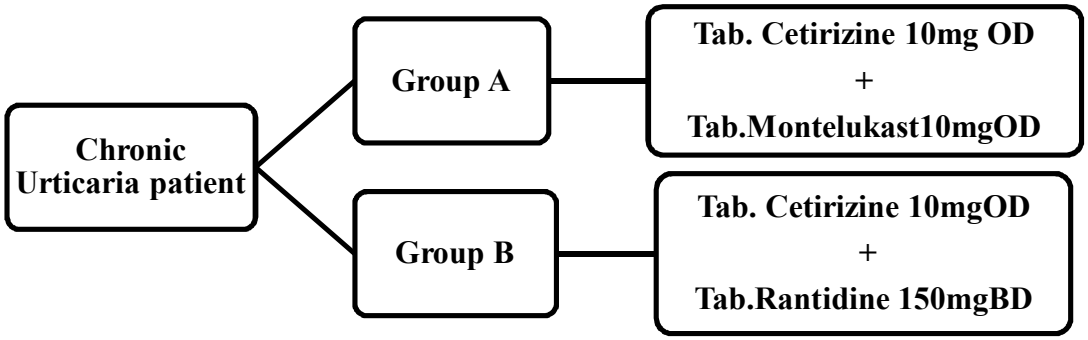
The study was conducted after obtaining the approval from Institutional Ethics Committee and conducted according to good clinical practice guidelines. Patients who fulfilled the selection criteria were recruited for the study from the outpatient department of Dermatology, Chengalpattu Medical College & Hospital. All patients were explained about the study purpose and procedures.

Written informed consent was obtained from all patients, in regional language in the prescribed format prior to the study. If the patient was illiterate, left thumb impression was sought. The demographic details of the patients were asked for and recorded.

Randomization

Among the 144 patients screened, 100 patients were recruited for the study. All odd number patients were assigned to group A (Cetirizine+ Montelukast) and even number patients were assigned to group B (Cetirizine +Ranitidine).

Treatment plan:



Complete history, clinical examination and baseline laboratory investigations were taken at the beginning of the study.

- **Group A** patients were asked to ingest tablet Cetirizine 10mg and tablet Montelukast 10mg once daily at night after food intake.
- **Group B** patients were instructed to take tablet Ranitidine 150mg twice daily 1hour before food in the morning and night along with tablet Cetirizine 10mg once daily at night after food intake.

Patients were educated to keep a daily record of urticaria activity score over 7 consecutive days in a descriptive chart provided to them. In that chart, patients were asked to circle the score that corresponds to the number of wheals they have and the score that represents the intensity of their pruritus (itching) on a daily basis. Daily, two times (morning and evening) patients scored pruritus, number of hives, over the preceding 12 hours (reflective) and soon at the time of assessment (instantaneous). These assessments were made on awakening (before dosing) and 12 hours after dosing.

Review of patient's completed record and clinical examinations of patients according to the Urticaria Activity Score7 (UAS7) were done at the end of every week. Sum of score were calculated at the end of every week for 4 weeks and the data recorded. Baseline laboratory investigations were repeated at the end of fourth week. Patients were followed up for 2 weeks after completion of the study.

Date	Daily number of wheals	+	Daily intensity of pruritus	=	Daily UAS score*
Example	0 (1) 2 3	+	0 1 (2) 3	=	0 1 2 (3) 4 5 6
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
					UAS7 score†

FIGURE 4: UAS ASSESSMENT CHART FOR PATIENTS

Assessment of efficacy:

The efficacy was assessed by the decrease in the weekly urticarial activity score which in turn shows the improvement in patient's symptomatology. Vital signs were monitored at all visits, whereas electrocardiography and laboratory tests were performed at screening and at the end of 4^{th} week and 6^{th} week .

Assessment of safety:

Patients were advised to report any occurrences of adverse events during treatment and follow up period and the same were recorded. Causality assessment of adverse drug reactions was done using WHO scale. Severity assessment was done by Modified Hartwig Seigel severity assessment scale. Safety evaluations included were any incidence of treatment-induced or any emergency adverse events, discontinuations due to adverse events, and changes from baseline in vital signs, laboratory parameters, and electrocardiographic intervals.

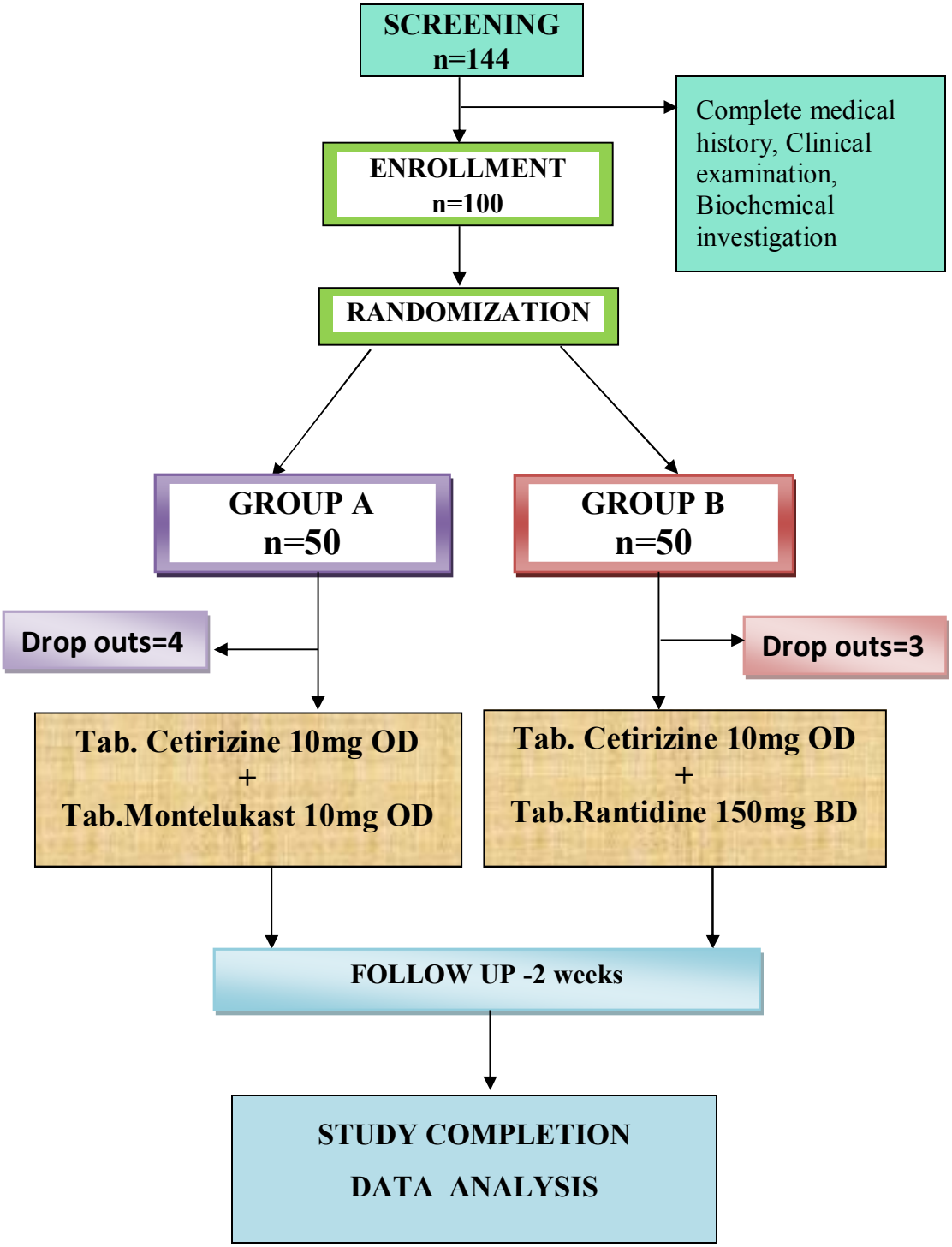


FIGURE 5 : STUDY FLOW CHART

TABLE 4 : DROP OUTS

	Group A	Group B
No. Of drop outs	4	3

Reasons for Drop Outs:

1. In Group A, one patient didn't turn up after 2 weeks of study, 3 patients lost follow up after 3 weeks of study.
2. In Group B, two patients didn't turn up after 1 week of study and one patient was not willing to continue in the study after 2 weeks .

STATISTICAL ANALYSIS

The details of the data collected were analyzed statistically using SPSS software (version 20) according to per protocol analysis. Hence, 93 patients who completed the study were included in the statistical analysis.

- Percentage distribution of age was analysed by Chi-square test and mean age distribution among the groups were analysed by student independent- t test.
- Analysis of sex distribution between groups was done by Chi- square test.
- The difference in mean urticaria activity score (UAS) every week within the same group for 4 weeks was analyzed using analysis of variance (ANOVA) whereas the difference in urticaria activity score (UAS) between group A and B assessed by student independent- t test.
- The biochemical investigations were done at baseline, week 4 and week 6. The difference in biochemical investigations within the groups before and after treatment was analyzed using student's paired t-test.
- The variations in biochemical investigations between group A and group B were analysed by student independent t-test.
- Percentage incidence of adverse effects among the study groups were analysed using Chi-square test.

Probability < 0.05 was considered to be statistically significant.

RESULTS

TABLE 5: AGE DISTRIBUTION

Age (in years)	Group A		Group B		Pearson Chi-square test
	n	%	n	%	
18- 30	12	26.09	17	36.17	X^2=1.57 P=0.6
31-40	16	34.78	14	29.79	
41-50	8	17.39	9	19.15	
51-60	10	21.74	7	14.89	
Total	46	100.0	47	100.0	

*P ≤ 0.05 significant,**P ≤ 0.01 highly significant, ***P ≤ 0.001 very high significant

Table 5 depict the demographic characteristics for age of the total population of 93 patients.

Highest number of patients lies between the age group of 18 – 40 years.

Using chi-square test, it was found that p = 0.6 and hence there exists **no significant statistical difference** in the percentage age distribution between the groups.

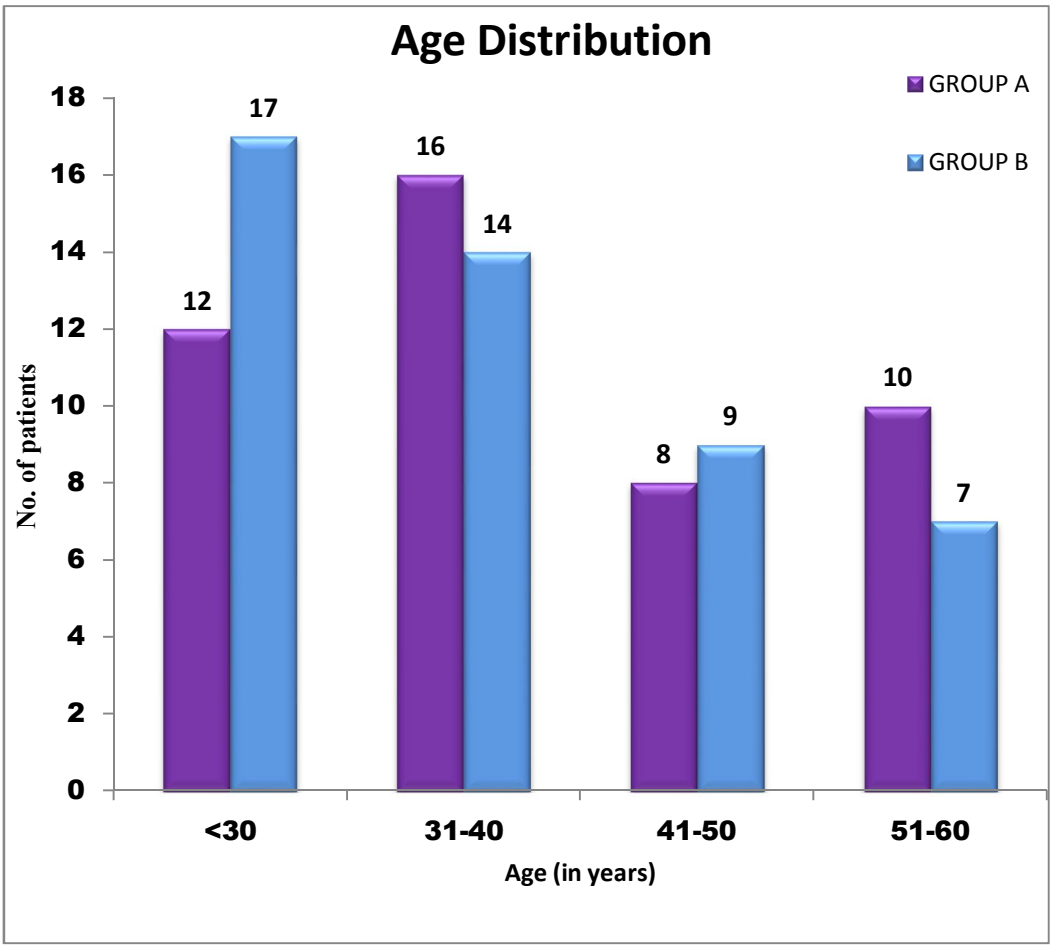


FIGURE 6 : AGE DISTRIBUTION AMONG THE STUDY GROUPS

Figure 6 shows the diagrammatic representation of the age distribution among the study groups.

TABLE 6: MEAN AGE DISTRIBUTION

Group	N	Mean	Std. Deviation	Student independent t-test
Group A	46	37.89	11.02	t = 0.618
Group B	47	36.40	12.13	P= 0.538

* P ≤ 0.05 significant, ** P ≤ 0.01 highly significant, *** P ≤ 0.001 very high significant

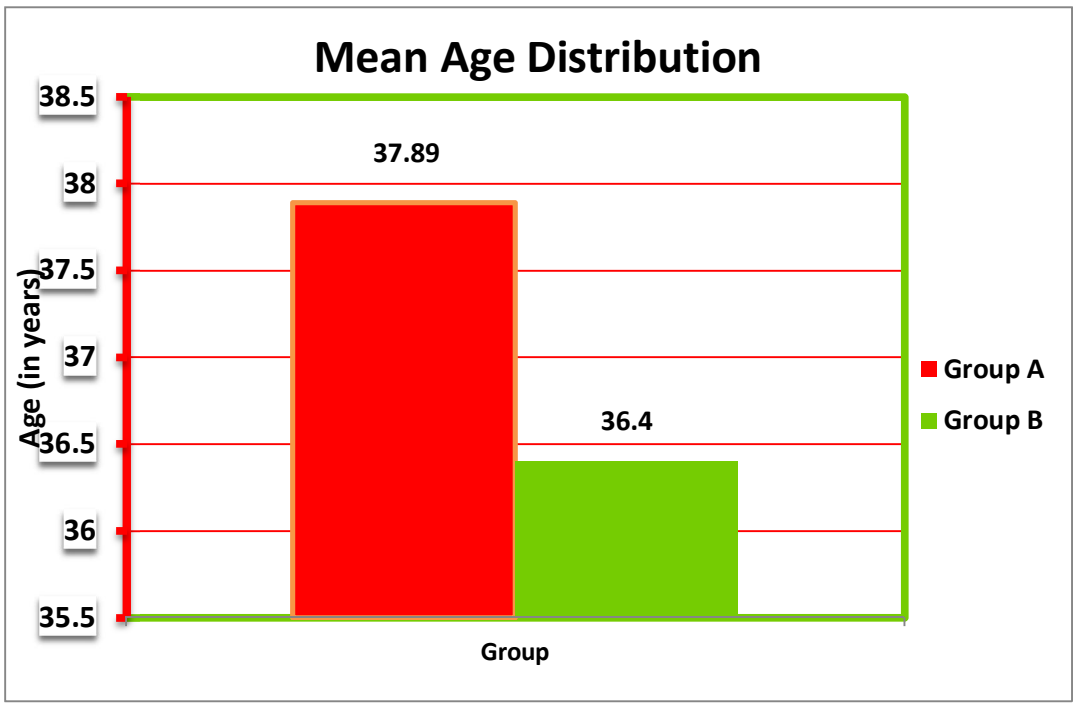


FIGURE 7 : MEAN AGE DISTRIBUTION

Table 6 & Figure 7 shows that

The mean age distribution was even in all the study groups.

There was **no significant difference** among the study groups.

TABLE 7: SEX DISTRIBUTION

Sex	Group A		Group B		Total	Pearson Chi-square test
	n	%	n	%		
Male	14	30.43	17	36.17	31	X^2=0.34 P = 0.5
Female	32	69.57	30	63.83	62	
Total	46	100	47	100	93	

* P ≤ 0.05 significant, ** P ≤ 0.01 highly significant, *** P ≤ 0.001 very high significant

Table 7 shows sex distribution.

There was a **predominance** of disease occurance in **female sex** in both the groups.

Incidence of disease among female sex was **twice** as common in males.

Statistical analysis was done by Chi square test. There was **no** statistically **significant difference** between groups regarding sex distribution.

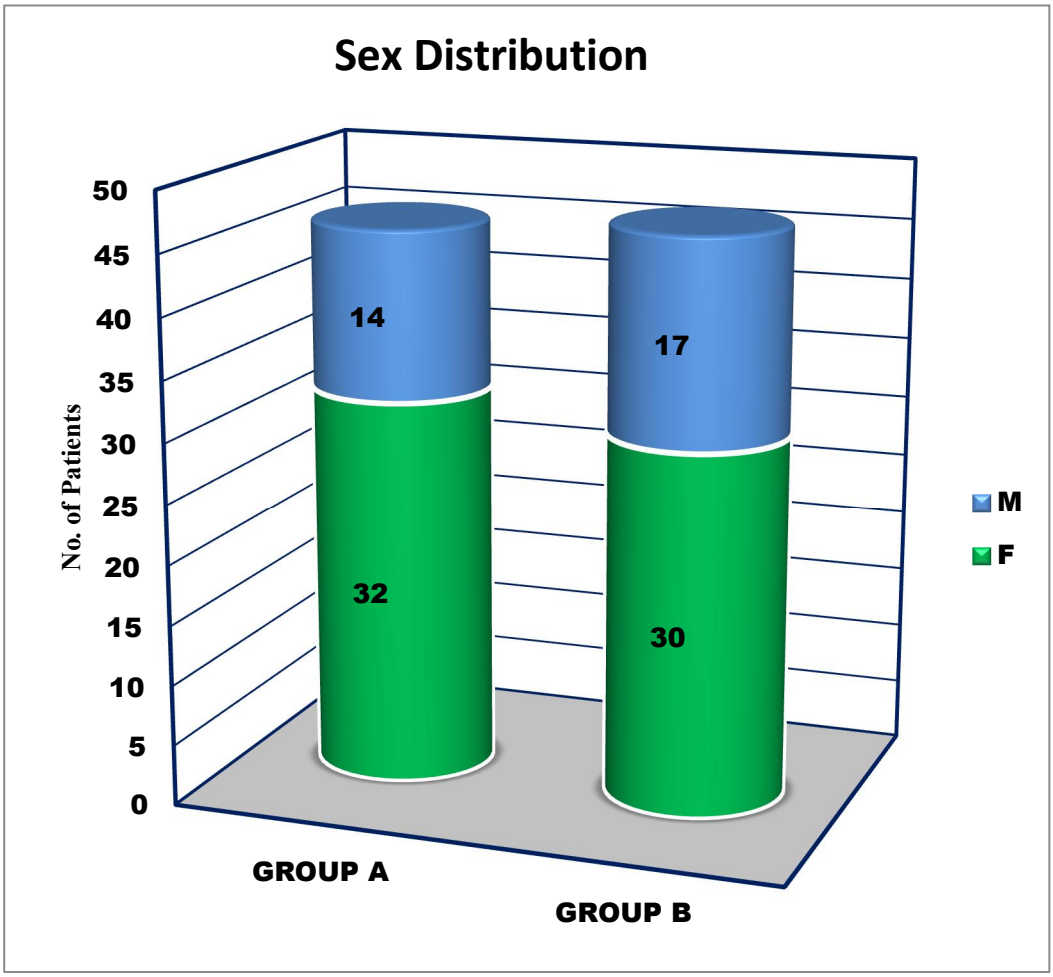


FIGURE 8 : SEX DISTRIBUTION

Figure 8 shows the bar diagram of sex distribution among the groups.

TABLE 8: MEAN DURATION OF URTICARIA (in months)

Group	N	Mean	Std. Deviation	Student independent t-test
Group A	46	8.35	5.313	t= 0.113 P= 0.91
Group B	47	8.23	4.335	

*P ≤ 0.05 significant, ** P ≤ 0.01 highly significant, *** P ≤ 0.001 very high significant

Table 8 depicts the mean duration of urticaria among the groups.

- Statistical analysis was done by student independent t-test and the mean duration of urticaria was 8 months in both the groups.
- There was no siginificant statistical difference among the groups.

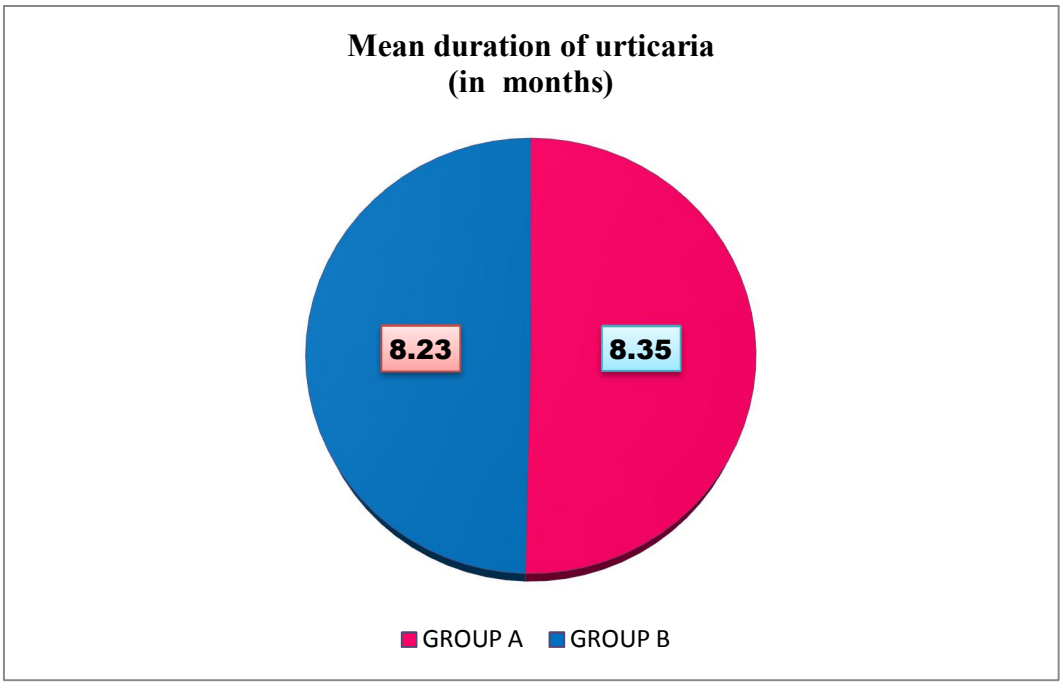


FIGURE 9 : MEAN DURATION OF URTICARIA

Figure 9 shows the pie diagram of mean duration of urticaria among the groups.

TABLE 9: WEEKLY URTICARIA ACTIVITY SCORE

UAS	Group A		Group B		Student independent t-test
	Mean	Std.Deviation	Mean	Std.Deviation	
Week 1	18. 78	4.765	27.57	7.512	t=6.723 P=0.0001***
Week 2	10.28	4.475	19.38	6.774	t=7.626 P=0.0001***
Week 3	4.87	4.631	13.91	6.971	t=7.354 P=0.0001***
Week 4	1.96	2.913	8.15	5.801	t=6.483 P=0.0001***

* $P \leq 0.05$ significant, ** $P \leq 0.01$ highly significant, *** $P \leq 0.001$ very high significant

Table 9 shows difference in weekly urticarial activity score between the groups.

- Statistical analysis by student independent t-test shows **significant difference** between groups in the urticaria activity score every week.
- Every week, mean urticaria activity score was found to be decreasing than previous week in both the groups but comparatively high in group B than group A in the same week. Hence, showing significant difference in the reduction of disease activity among the groups.

TABLE 10: WEEKLY URTICARIA ACTIVITY SCORE

GROUP A:

UAS	No. of patients	Mean	Std. Deviation	Test of significance (ANOVA)
Week 1	**46**	**18.78**	**4.765**	**F=138.421 p=0.0001*** **
Week 2	**46**	**10.28**	**4.475**	
Week 3	**46**	**4.87**	**4.631**	
Week 4	**46**	**1.96**	**2.913**	
TOTAL	**184**	**8.97**	**7.687**	

* P ≤ 0.05 significant, ** P ≤ 0.01 highly significant, *** P ≤ 0.001 very high significant

Table 10 statistical analysis of mean UAS by ANOVA in **group A** over 4 weeks shows **significant difference** every week within the group.

TABLE 11: WEEKLY URTICARIA ACTIVITY SCORE

GROUP B:

UAS	No. of patients	Mean	Std. Deviation	Test of significance (ANOVA)
Week 1	**47**	**27.57**	**7.512**	**F= 69.636 p=0.0001*** **
Week 2	**47**	**19.38**	**6.774**	
Week 3	**47**	**13.91**	**6.971**	
Week 4	**47**	**8.15**	**5.801**	
TOTAL	**188**	**17.26**	**9.846**	

* P ≤ 0.05 significant, ** P ≤ 0.01 highly significant, *** P ≤ 0.001 very high significant

Table 11 statistical analysis of mean UAS by ANOVA in **group B** over 4 weeks shows **significant difference** every week within the group.

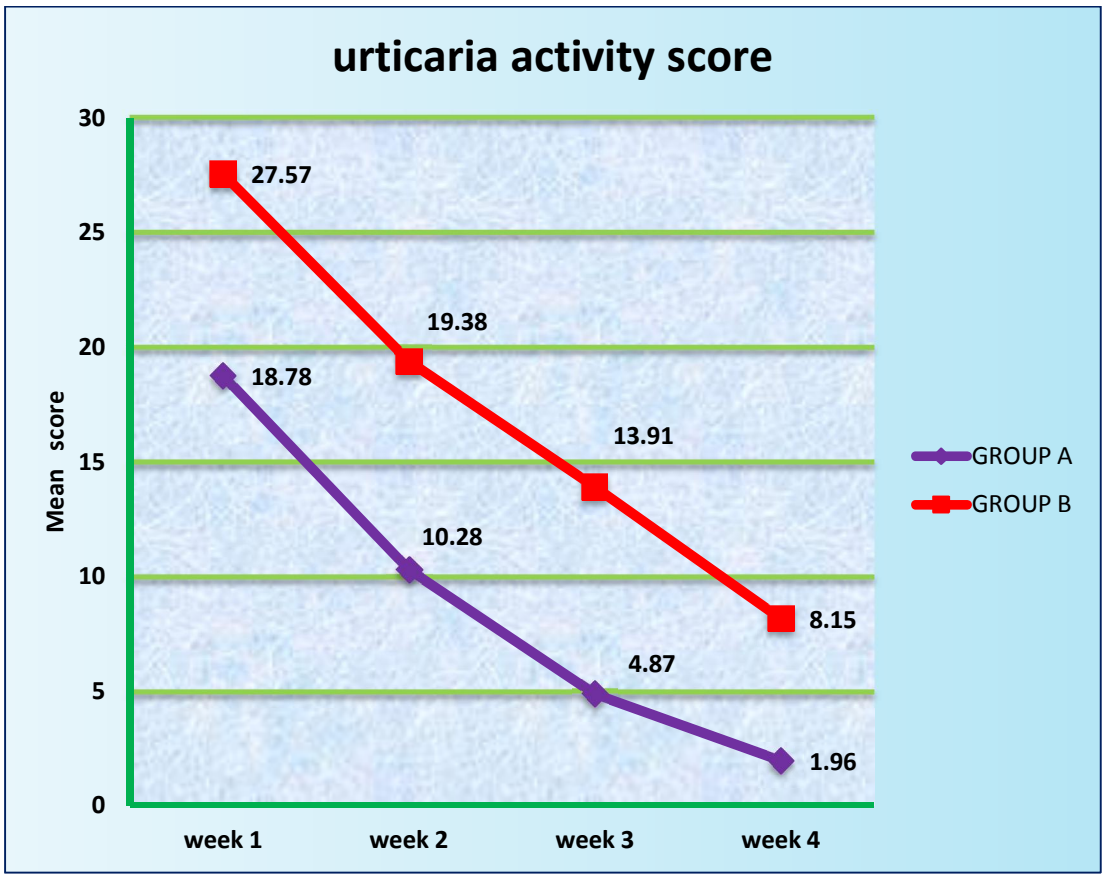


FIGURE 10 : URTICARIA ACTIVITY SCORE

Figure 10 shows the diagrammatic representation of mean weekly urticaria activity score reduction in each group at the end of 1st week, 2nd week, 3rd week and 4th week respectively.

TABLE 12: TOTAL URTICARIA SCORE

Group	n	Mean	Std. Deviation	Student independent t-test
Group A	46	35.89	14.49	t = 8.629 P = 0.0001***
Group B	47	69.02	21.739	

* P ≤ 0.05 significant, ** P ≤ 0.01 highly significant, *** P ≤ 0.001 very high significant

Table 12 shows mean total urticaria score between group A and group B, showing significant difference by student independent t-test.

Group A shows lesser mean total urticaria score implying a decrease in disease activity compared to group B.

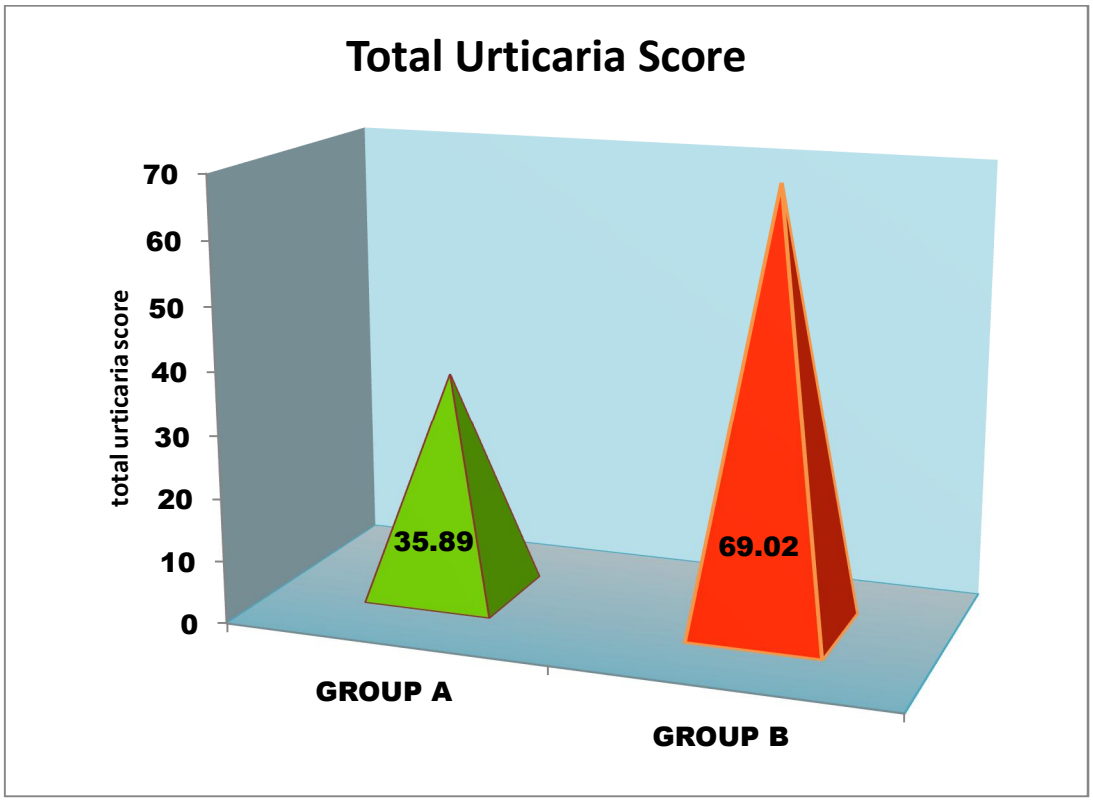


FIGURE 11 TOTAL URTICARIA SCORE

Figure 11 depicts the difference in the reduction of mean total urticaria score between group A and group B.

TABLE 13a: HAEMOGLOBIN

HEMOGLOBIN	Group A		Group B		Student independent t- test
	Mean	Std.Deviation	Mean	Std. Deviation	
Baseline	10.241	1.1577	10.06	1.0421	t=0.796 p=0.428
Week 4	10.339	0.9985	10.145	1.0123	t=0.932 p=0.354
Week 6	10.591	1.1333	10.394	1.2368	t=0.803 P=0.424

* P ≤ 0.05 significant, ** P ≤ 0.01 highly significant, *** P ≤ 0.001 very high significant

Table 13a shows the haemoglobin level at baseline, end of week 4 and end of week 6 in groups A and B.

The differences in haemoglobin level analysed by student independent t-test were **not statistically significant** between the groups.

TABLE 13b: HEMOGLOBIN

HEMO-GLOBIN	Group A				Group B			
	baseline	4th week	baseline	6th week	baseline	4th week	baseline	6th week
Mean	10.241	10.339	10.241	10.591	10.06	10.145	10.06	10.394
Standard deviation	1.1577	0.9985	1.1577	1.1333	1.0421	1.0123	1.0421	1.2368
Student paired t-test	t=1.415 p=0.164		t=1.364 p=0.179		t=0.937 p=0.353		t=1.473 p=0.147	

* P ≤ 0.05 significant, ** P ≤ 0.01 highly significant, *** P ≤ 0.001 very high significant

Table 13b shows the difference in haemoglobin level before and after drug administration in both the groups.

Using student paired t-test for analysis, it was found that there was **no significant difference** between baseline, 4th week and 6th week haemoglobin values in both the groups.

TABLE 14a: TOTAL LEUCOCYTE COUNT (TLC)

TLC	Group A		Group B		Student independent t- test
	Mean	Std.Deviation	Mean	Std. Deviation	
Baseline	6905.22	863.734	6922.32	929.308	t= 0.092 p= 0.927
Week 4	6831.43	1015.367	6785.38	653.717	t= 0.261 p=0.795
Week 6	6567.74	725.573	6707.34	800.236	t= 0.881 p= 0.381

* P ≤ 0.05 significant, ** P ≤ 0.01 highly significant, *** P ≤ 0.001 very high significant

Table 14a shows the total leucocyte count at baseline, end of week 4 and end of week 6 in groups A and B.

The differences in the total leucocyte count analysed by student independent t-test were not statistically significant between the groups.

TABLE 14b: TOTAL LEUCOCYTE COUNT

TLC	Group A				Group B			
	baseline	4th week	baseline	6th week	baseline	4th week	baseline	6th week
Mean	6905.22	6831.4	6905.22	6567.7	6922.32	6785.3	6922.3	6702.3
Standard deviation	863.73	1015.3	863.734	725.57	929.30	653.71	929.30	800.23
Student paired t-test	t=0.772 p=0.444		t=2.068 p=0.524		t=2.017 p=0.481		t=1.23 p=0.225	

* P ≤ 0.05 significant, ** P ≤ 0.01 highly significant, *** P ≤ 0.001 very high significant

Table 14b shows the difference in total leucocyte count before and after drug administration in both the groups.

Using student paired t-test for analysis, it was found that there was **no significant difference** between baseline, 4th week and 6th week total leucocyte count values in both the groups.

TABLE 15a: ERYTHROCYTE SEDIMENTATION RATE (ESR)

ESR	Group A		Group B		Student independent t- test
	Mean	Std.Deviation	Mean	Std. Deviation	
Baseline	10.77	1.679	10.69	1.781	t= 0.224 p=0.824
Week 4	10.539	1.3668	10.411	1.6469	t=0.409 p=0.684
Week 6	10.626	1.5564	10.568	1.6706	t=0.173 p=0.863

* P ≤ 0.05 significant, ** P ≤ 0.01 highly significant, *** P ≤ 0.001 very high significant

Table 15a shows the erythrocyte sedimentation rate at baseline, end of 4th week and end of 6th week in groups A and B.

The differences in the erythrocyte sedimentation rate analysed by student independent t-test were **not statistically significant** between the groups.

TABLE 15b: ERYTHROCYTE SEDIMENTATION RATE

ESR	Group A				Group B			
	baseline	4th week	baseline	6th week	baseline	4th week	baseline	6th week
Mean	10.77	10.77	10.77	10.77	10.69	10.411	10.69	10.568
Standard deviation	1.679	1.679	1.679	1.679	1.781	1.647	1.781	1.671
Student paired t-test	t=1.877 p=0.067		t=0.409 p=0.684		t=-1.934 p=0.059		t=0.374 p=0.71	

* P ≤ 0.05 significant, ** P ≤ 0.01 highly significant, *** P ≤ 0.001 very high significant

Table 15b shows the difference in erythrocyte sedimentation rate before and after drug administration in both the groups.

Student paired t-test was used for analysis, and there was **no significant difference** between baseline, 4th week and 6th week erythrocyte sedimentation rate values in both the groups.

TABLE 16 a: EOSINOPHIL COUNT

Eosinophil count	Group A		Group B		Student independent t- test
	Mean	Std.Deviation	Mean	Std. Deviation	
Baseline	7.7	2.25	7.85	2.485	t=0.316 p=0.753
Week 4	7.57	2.136	7.51	2.145	t=0.123 p=0.902
Week 6	7.59	2.464	7.72	2.243	t=0.279 p=0.781

* P ≤ 0.05 significant, ** P ≤ 0.01 highly significant, *** P ≤ 0.001 very high significant

Table 16a shows the eosinophil count at baseline, end of week 4 and end of week 6 in groups A and B.

The differences in the eosinophil count analysed by student independent t-test were **not statistically significant** between the groups though there was little decrease in the eosinophil count at week 4 and 6 compared to baseline.

TABLE 16b: EOSINOPHIL COUNT

EOSINOPHIL COUNT	Group A				Group B			
	baseline	4th week	baseline	6th week	baseline	4th week	baseline	6th week
Mean	7.7	7.57	7.7	7.59	7.85	7.51	7.85	7.72
Standard deviation	2.25	2.136	2.25	2.464	2.485	2.145	2.485	2.243
Student paired t-test	t=0.275 p=0.784		t=0.197 p=0.845		t=0.751 p=0.268		t=0.268 p=0.79	

* P ≤ 0.05 significant, ** P ≤ 0.01 highly significant, *** P ≤ 0.001 very high significant

Table 16b shows the difference in eosinophil count before and after drug administration in both the groups.

Using student paired t-test for analysis, it was found that there was **no significant difference** in the eosinophil count between baseline, 4th week and 6th week values in both the groups.

TABLE 17a: PLATELET COUNT

Platelet count	Group A		Group B		Student independent t- test
	Mean	Std.Deviation	Mean	Std. Deviation	
Baseline	2.53	0.3	2.48	0.256	t=0.902 p=0.369
Week 4	2.513	0.319	2.52	0.3516	t=0.106 p=0.916
Week 6	2.497	0.296	2.5	0.3016	t=0.046 p=0.964

* P ≤ 0.05 significant, ** P ≤ 0.01 highly significant, *** P ≤ 0.001 very high significant

Table 17a shows the Platelet count at baseline, end of week 4 and end of week 6 in groups A and B.

The differences in the Platelet count analysed by student independent t-test were **not statistically significant** between the groups .

TABLE 17b: PLATELET COUNT

PLATELET COUNT	Group A				Group B			
	baseline	4th week	baseline	6th week	baseline	4th week	baseline	6th week
Mean	2.53	2.5126	2.53	2.4972	2.48	2.48	2.48	2.48
Standard deviation	0.3	0.3192	0.3	0.296	0.256	0.352	0.256	0.302
Student paired t-test	t=0.247 p=0.806		t=0.473 p=0.639		t=0.705 p=0.484		t=0.387 p=0.701	

* P ≤ 0.05 significant, ** P ≤ 0.01 highly significant, *** P ≤ 0.001 very high significant

Table 17b shows the difference in Platelet count t before and after drug administration in both the groups.

Using student paired t-test for analysis, it was found that there was **no significant difference** in the Platelet count t between baseline, 4th week and 6th week values in both the groups.

TABLE 18 a: BLOOD SUGAR

BLOOD SUGAR	Group A		Group B		Student independent t- test
	Mean	Std.Deviation	Mean	Std. Deviation	
Baseline	95.61	15.826	98.85	13.48	t=1.63 P=0.19
Week 4	96.07	12.447	97.07	13.31	t=1.28 p=0.28
Week 6	93.85	9.71	97.59	9.49	t=1.75 p=0.18

* P ≤ 0.05 significant, ** P ≤ 0.01 highly significant, *** P ≤ 0.001 very high significant

Table 18a shows the mean blood sugar values at baseline, end of week 4 and end of week 6 in groups A and B.

The differences in the blood sugar values analysed by student independent t-test were **not statistically significant** between the groups

TABLE 18 b: BLOOD SUGAR

BLOOD SUGAR	Group A				Group B			
	baseline	4th week	baseline	6th week	baseline	4th week	baseline	6th week
Mean	95.61	96.07	95.61	93.85	98.85	97.07	98.85	97.59
Standard deviation	15.826	12.447	15.826	9.71	13.48	13.31	13.48	9.49
Student paired t-test	t=0.28 p=0. 85		t=0.17 p=0.92		t=0.49 p=0.69		t=0.09 p=0.96	

* P ≤ 0.05 significant, ** P ≤ 0.01 highly significant, *** P ≤ 0.001 very high significant

Table 18b shows the difference in blood sugar values before and after drug administration in both the groups.

Using student paired t-test for analysis, it was found that there was **no significant difference** in the blood sugar values between baseline, 4th week and 6th week values in both the groups.

TABLE 19a: SERUM CREATININE

Serum creatinine	Group A		Group B		Student independent t-test
	Mean	Std.Deviation	Mean	Std. Deviation	
Baseline	0.7348	0.0508	0.7338	0.0478	t=0.093 p=0.926
Week 4	0.73	0.068	0.74	0.036	t=1.021 p=0.31
Week 6	0.7274	0.05874	0.7211	0.0574	t=0.525 p=0.601

* P ≤ 0.05 significant, ** P ≤ 0.01 highly significant, *** P ≤ 0.001 very high significant

Table 1a shows the mean serum creatinine values at baseline, end of week 4 and end of week 6 in groups A and B.

The differences in the serum creatinine values analysed by student independent t-test were **not statistically significant** between the groups .

TABLE 19b: SERUM CREATININE

SERUM CREATININE	Group A				Group B			
	baseline	4th week	baseline	6th week	baseline	4th week	baseline	6th week
Mean	0.735	0.73	0.735	0.727	0.734	0.74	0.734	0.721
Standard deviation	0.0508	0.068	0.0508	0.058	0.0478	0.036	0.0478	0.057
Student paired t-test	t=0.408 p=0.685		t=0.631 p=0.531		t=0.842 p=0.404		t=1.162 p=0.251	

* P ≤ 0.05 significant, ** P ≤ 0.01 highly significant, *** P ≤ 0.001 very high significant

Table 19b shows the difference in serum creatinine before and after drug administration in both the groups.

Using student paired t-test for analysis, it was found that there was **no significant difference** in the serum creatinine between baseline, 4th week and 6th week values in both the groups.

TABLE 20a: BLOOD UREA

Blood urea	Group A		Group B		Student independent t-test
	Mean	Std.Deviation	Mean	Std. Deviation	
Baseline	21.78	1.685	21.7	1.366	t=0.253 p=0.801
Week 4	21.91	1.488	22.09	1.792	t=0.503 p=0.616
Week 6	21.89	1.676	21.91	1.516	t=0.071 p=0.943

* P ≤ 0.05 significant, ** P ≤ 0.01 highly significant, *** P ≤ 0.001 very high significant

Table 20a shows the mean blood urea values at baseline, end of week 4 and end of week 6 in groups A and B.

The differences in the blood urea values analysed by student independent t-test were **not statistically significant** between the groups.

TABLE 20b: BLOOD UREA

Blood urea	Group A				Group B			
	baseline	4th week	baseline	6th week	baseline	4th week	baseline	6th week
Mean	21.78	21.91	21.78	21.89	21.7	21.7	21.7	21.7
Standard deviation	1.685	1.488	1.685	1.676	1.366	1.366	1.366	1.366
Student paired t-test	t= 0.395 p= 0.694		t= 0.343 p=0.734		t= 1.176 p=0.245		t=0.798 p= 0.429	

* P ≤ 0.05 significant, ** P ≤ 0.01 highly significant, *** P ≤ 0.001 very high significant

Table 20b shows the difference in blood urea before and after drug administration in both the groups.

Using student paired t-test for analysis, it was found that there was **no significant difference** in the blood urea values between baseline, 4th week and 6th week values in both the groups.

TABLE 21a: SGOT

SGOT	Group A		Group B		Student independent t- test
	Mean	Std.Deviation	Mean	Std. Deviation	
Baseline	14.72	2.177	14.72	2.411	t=0.013 p=0.99
Week 4	14.39	1.807	14.45	2.124	t=0.136 p=0.892
Week 6	14.35	2.152	14.79	1.731	t=1.086 p=0.28

* P ≤ 0.05 significant, ** P ≤ 0.01 highly significant, *** P ≤ 0.001 very high significant

Table 21a shows the mean SGOT values at baseline, at the end of week 4 and at the end of week 6 in groups A and B.

The differences in the SGOT values analysed by student independent t-test were **not statistically significant** between the groups.

TABLE 21b: SGOT

SGOT	Group A				Group B			
	baseline	4th week	baseline	6th week	baseline	4th week	baseline	6th week
Mean	14.72	14.39	14.72	14.35	14.72	14.45	14.72	14.79
Standard deviation	2.177	1.807	2.177	2.152	2.411	1.124	2.411	1.731
Student paired t-test	t=0.778 p=0.441		t=0.822 p=0.416		t=0.597 p=0.553		t=0.142 p=0.887	

* P ≤ 0.05 significant, ** P ≤ 0.01 highly significant, *** P ≤ 0.001 very high significant

Table 21b shows the difference in the SGOT before and after drug administration in both the groups.

Using student paired t-test for analysis, it was found that there was **no significant difference** in the SGOT values between baseline, 4th week and 6th week values in both the groups.

TABLE 22a: SGPT

SGPT	Group A		Group B		Student independent t- test
	Mean	Std.Deviation	Mean	Std. Deviation	
Baseline	16.2	2.125	16.98	2.982	t=1.456 p=0.149
Week 4	16.26	2.408	16.85	2.274	t=1.215 p=0.227
Week 6	16.15	2.357	16.7	2.82	t=1.019 p=0.311

* P ≤ 0.05 significant, ** P ≤ 0.01 highly significant, *** P ≤ 0.001 very high significant

Table 22a shows the SGPT values at baseline, end of week 4 and end of week 6 in groups A and B.

The differences in the SGPT values analysed by student independent t-test were **not statistically significant** between the groups.

TABLE 22b: SGPT

SGPT	Group A				Group B			
	baseline	4th week	baseline	6th week	baseline	4th week	baseline	6th week
Mean	16.2	16.26	16.2	16.15	16.98	16.85	16.98	16.7
Standard deviation	2.125	2.408	2.125	2.357	2.982	2.274	2.982	2.82
Student paired t-test	t=0.133 p=0.894		t=0.095 p=0.924		t= 0.268 p= 0.79		t= 0.454 p= 0.652	

* P ≤ 0.05 significant, ** P ≤ 0.01 highly significant, *** P ≤ 0.001 very high significant

Table 22b shows the difference in SGPT values before and after drug administration in both the groups.

Using student paired t-test for analysis, it was found that there was **no significant difference** in the SGPT values between baseline, 4th week and 6th week values in both the groups.

TABLE 23: INCIDENCE OF ADVERSE EVENTS

	GROUP A	GROUP B
NUMBER OF ADRs	**11**	**8**

TABLE 24: ADVERSE EVENTS

ADVERSE EVENTS	GROUP A		GROUP B		Chi square test	p- value
	Number of patients	%	number of patients	%		
Sedation	**7**	**14%**	**4**	**8%**	**0.9**	**0.30**
Dizziness	**3**	**6%**	**2**	**4%**	**0.2**	**0.60**
Headache	**1**	**2%**	**2**	**4%**	**0.3**	**0.50**

* P ≤ 0.05 significant, ** P ≤ 0.01 highly significant, *** P ≤ 0.001 very high significant

Table 23 & 24 shows the Adverse events reported in both groups. The adverse events were mild and no serious adverse effects were reported. Among the adverse events, it was found that sedation was the most common followed by dizziness and headache.

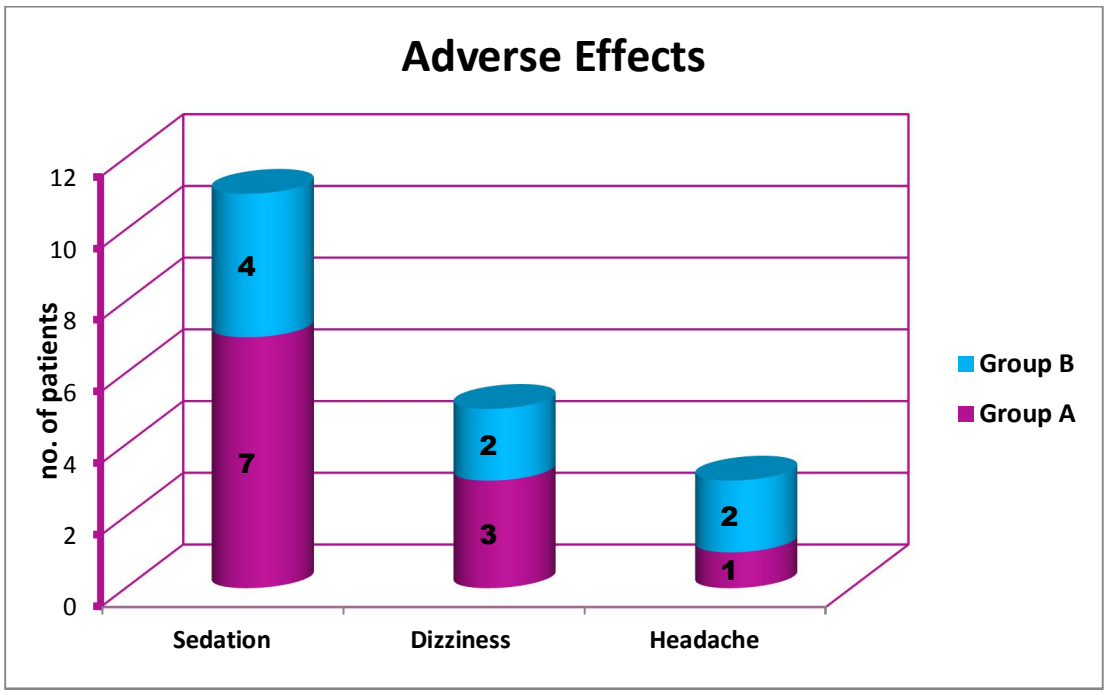


FIGURE 12 : ADVERSE EFFECTS

Figure 12 shows number of adverse events in both groups.

DISCUSSION

Chronic urticaria, known since ancient times, is a highly distressing disease that can invariably disturb a person's personal, social and occupational life altogether. This chronic disease manifests as pruritic, raised wheals of reddish colour all over the body of varying sizes with serpiginous margins with blanched centers which may coalesce sometimes [58]. It may appear daily or on most days of a week for a duration of greater than 6 weeks.

Apart from identifying the trigger factor and avoiding it, to aim for complete control of symptom in urticaria as safely as possible is the current recommendation by the EAACI/GA2LEN/EDF/WAO guideline. The treatment of chronic urticaria remains a challenging task for physicians. A step-wise approach is currently advocated by the 2009 treatment guidelines [34]. First line therapy comprises a non-sedating H_1-antihistamine at standard doses. After two weeks, if no response is obtained, the dose has to be increased up to four times the standard or licensed dose.

Third line of therapy includes the addition of a leukotriene receptor antagonist (LTRA). For severe or resistant cases, immunosuppressants such as ciclosporin, dapsone, H2-antihistamines and omalizumab [97] are also used. Short-course systemic steroids are recommended for exacerbations.

From India, there are no published studies regarding the use of montelukast in urticaria. Though it is known that monotherapy with montelukast is probably not advisable, there is a need for validation in the Indian population, regarding the outcome of addition of montelukast to an antihistamine in patients with chronic urticaria.

Similarly, datas about the efficacy of H_2 blockers as an additional therapy to antihistamines in treating chronic urticaria are limited. The combined effect of H_1-H_2 antihistamines is more due to interactions at the CYP3A4 level or other isoenzyme families - resulting in mutual increase in the area under the plasma concentration-time curve (AUC) – rather than due to any genuine "synergic effect".

In a study by Watson *et al*, it is said that famotidine combined with diphenhydramine shown better symptom improvement in chronic urticaria than prescribing diphenhydramine alone [(102)].

There are not enough confirmatory data from clinical trials to recommend combination of 2nd generation antihistamines with leukotriene antagonists or H_2 blockers; the role of these drugs in chronic urticaria remains to be established.

Hence the study was undertaken with the aim to compare the efficacy and safety of the combination therapy of montelukast and cetirizine with ranitidine and cetirizine in chronic urticaria in a tertiary care hospital.

The study was conducted in the Outpatient Department of dermatology, Chengalpattu Medical College and Hospital, Chengalpattu.

Out of 144 patients screened, 100 patients who fulfilled the inclusion and exclusion criteria were recruited for the study. They were randomized into two groups, Group A and Group B, each group consisting of 50 patients. Patients in Group A received tablet Cetirizine 10mg and Tab.Montelukast 10mg once daily at night after food intake. Group B patients received tablet Ranitidine 150mg twice daily 1 hour before food in the morning and night along with tablet Cetirizine 10mg once daily at night after food intake.

Urticaria activity score which is the efficacy variable in this study was plotted by the patient daily and reviewed weekly for four weeks. At the end of fourth week, sum of scores i.e, total of the weekly urticaria activity score was calculated. Biochemical investigations such as complete hemogram, blood sugar, blood urea, serum creatinine, SGOT, SGPT were estimated at the baseline , at the end of 4^{th} week and at the end of 2 weeks follow up period. i.e, 6^{th} week. Data were compiled and results analyzed statistically.

Regarding demographic characteristics, parameters such as age distribution and sex distribution were taken into account and analyzed for any statistical significance and found to have no statistical significance between the study groups in demographic characteristics.

Among the 93 patients with chronic urticaria who completed the study, the mean age in group A was 37.9 years and 36.4 years in group B. More than 60% of subjects in both groups were female, reflecting a higher disease incidence among female subjects.

The mean duration of urticaria among the study subjects in group A and group B were 7.93 and 8.11 months respectively.

In our study, efficacy outcome measured by the mean weekly urticaria activity score (UAS) at the end of $1^{st,}$ 2^{nd}, 3^{rd} and 4^{th} week among group A were 18.67, 10.07, 4.65, 1.74 respectively. The mean UAS among group B at the end of $1^{st,}$ 2^{nd}, 3^{rd} and 4^{th} week were 27.77, 19.38, 13.68 and 8.04 respectively. This shows that there exists significant difference in the reduction of urticarial symptoms between group A receiving montelukast add-on therapy and group B receiving ranitidine add-on therapy, with group A showing a favourable result. Every week, mean urticaria activity score was found to be decreasing than previous week in both the groups but comparatively high values were seen in group B than group A in the same week. Hence, showing significant difference in the reduction of disease activity among the study groups.

The mean total urticaria activity score among montelukast group is 35.13 whereas that among ranitidine group is 68.87 ($p< 0.001$) showing significant reduction in wheals and pruritus among group A compared to group B. This is consistent with the findings of a double blind cross over study conducted by M. Kosnik & T. Subic who showed that response to add-on treatment with montelukast was seen among patients with particularly long

standing disease [103]. Similar to his study, in our study, we included only patients with prolonged duration of illness who failed to respond to cetirizine alone and obtained similar results.

In a study by Wan *et al*, lesser response rate with montelukast add on to loratidine vs loratidine alone therapy was reported ,but this study in contrast to our study was conducted in newly diagnosed chronic urticaria patients [14].

Hence, most patients are antihistamine responsive and their major pathological mediator being histamine and not leukotrienes which might have skewed the results of this studies towards relative poor response with add on montelukast.

A pronounced favourable response to montelukast, especially in aspirin intolerant chronic urticaria patients were reported by Pacor *et al* and erbagci Z *et al* [104, 73].

Our safety outcome measures like hematological and biochemical parameters were measured at the baseline, at the end of 4th week, and at the end of 6th week. Inter and intra group varaiations of the parameters analysed by student t-test showing no statistical difference among the study groups implies that both the drugs doesn't have any untoward effects on these parameters. ECG and chest X-ray taken at the beginning and at the end of the study had no significant variations.

A lower incidence of adverse events was encountered in the study. All adverse events were rated as mild. Mild adverse effects such as sedation, dizziness and headache occurred among study groups which does not show any statistical significant difference among the groups and all the adverse effects subsided without any medications.

After the completion of study period, patients were asked to report to the OPD after 2 weeks for follow up. All the patients were evaluated clinically. Relapse of urticarial symptoms was reported in 5 patients in the group treated with montelukast and in 14 patients in the group treated with ranitidine during the follow up period of 2 weeks. This shows the good number of remission attained in group A compared to group B.

The results of this study demonstrate that montelukast administered 10 mg once daily as an add-on therapy to cetirizine 10 mg once daily is more effective than ranitidine 150mg twice daily add on therapy for the treatment of urticarial symptoms in patients with chronic urticaria.

Thus, montelukast can be safely used in combination with antihistamines for chronic urticaria patients whose response is poor to antihistamines alone.

LIMITATIONS

Limitations of our study include smaller number of study subjects; stratification based on severity of chronic urticaria was not done; effect on quality of life was not evaluated separately.

It is worth to give a trial of montelukast as add on medication in chronic urticaria patients. However, a trial including a larger group of Indian population is recommended.

CONCLUSION

From our study, we conclude that

Combination therapy of Montelukast and Cetirizine is found to be more efficacious than Ranitidine and Cetirizine in the treatment of chronic urticaria patients not responding to cetirizine alone. This is evidenced by statistically significant difference in UAS ($p<0.05$) between montelukast group and ranitidine group. Hence, montelukast was found to be an effective adjuvant to cetirizine in chronic urticaria. In view of safety, Montelukast was well tolerated with lesser side effect profiles.

Relapse of symptoms was found to be more in ranitidine group than in montelukast group during the follow up period further favouring therapeutic effect of montelukast.

Thus, Montelukast seems to be a promising medication both in the aspect of efficacy as well as safety in patients with chronic urticaria.

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Annexures

PROFORMA

Serial No:

Name: **Hospital No:**

1: Age: **Sex:** **a: male** **b: female**

4: Socio economic class: L/ M/ H

- Present History:
  Time of onset of disease:
  Frequency:
  Duration:
  Diurnal variation:
  Relation to food:
- past history :
- history of use of any other drugs
- family history of urticaria/atopy

General Examination:

Heart rate :
Blood Pressure :
Respiratory :

Systemic Examination

- CVS :
- RS :
- Abdomen :
- CNS :

Urticaria Severity Assessment:

WEEK 1		DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
	Wheals							
	pruritis							

WEEK 2		DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
	Wheals							
	pruritis							

WEEK 3		DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
	Wheals							
	pruritis							

WEEK 4		DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
	Wheals							
	pruritis							

Response to treatment:

SUM OF SCORE			
Week 1	Week 2	Week 3	Week 4
TOTAL:			

LABORATORY INVESTIGATIONS

Parameters	Baseline	4th week	6th week
Hb%			
Total count			
Eosinophil Count			
ESR			
Platelet count			
SGPT			
SGOT			
Blood Sugar			
Blood urea			
Serum creatinine			

ECG:

X-RAY:

UAS ASSESSMENT CHART FOR PATIENTS:

Date	Daily number of wheals	+	Daily intensity of pruritus	=	Daily UAS score*
Example	0 ① 2 3	+	0 1 ② 3	=	0 1 2 ③ 4 5 6
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
					UAS7 score†

INFORMED CONSENT FORM

Title of the study :"**A prospective, randomized, open label, comparative study of Montelukast and Ranitidine as an add on therapy to Cetirizine in chronic urticaria**"

Name of the participant :

Name of the Investigator : Dr. S.SWEETLIN

Name of the Institution : Chengalpattu Medical College/ Hospital

Documentation of the informed consent.

I _____have read the information in this form (or it has been read to me).I was free to ask any questions and they have been answered. I am over 18 years of age and, exercising my free power of choice, hereby give my consent to be included as a participant in "**A PROSPECTIVE, RANDOMIZED, OPEN LABEL, COMPARATIVE STUDY OF MONTELUKAST AND RANITIDINE AS AN ADD ON THERAPY TO CETIRIZINE IN CHRONIC URTICARIA**"

1. I have read and understand this consent form and the information provided to me.
2. I have had the consent document explained to me.
3. I have been explained about the nature of the study.
4. I have been explained about my rights and responsibilities by the investigator.
5. I have been informed the investigator of all the treatments I am taking or have taken in the past_____including any native (alternative) treatment.
6. I have been advised about the risks associated with my participation in this study.
7. I agree to cooperate with the investigator and I will inform him/her immediately if I suffer unusual symptoms.
8. I have not participated in any research study within the past_____.
9. I have not donated blood within the past_____- Add if the study involves extensive blood sampling.
10. I am aware of the fact that I can opt out of the study at any time without having to give any reason and this will not affect my future treatment in this hospital.
11. I am also aware that the investigator may treatment my participated in the study at any time for any reason, without my consent.
12. I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to the sponsors, regulatory authorities, Govt.Agencies, and IEC. I understand that they are publicly presented.
13. I have understood that my identity will be kept confidential if my data are publicly presented.
14. I have had my questions answered to my satisfaction.
15. I have decided to be in the research study.

I am aware that if I have any question during this study, I should contact the Investigator. By signing this consent form I attest that the information given in this document has been clearly explained to me and understood by me, I will be given a copy of this consent document.

For adult participants:

Name and signature/thumb impression of the participant (or legal representative if participant incompetent)

Name_____signature_____Date_____

Name and signature of impartial witness (require for illiterate patients)

Name_____signature_____Date_____

Address and contact number of the impartial witness:

_____

Name and signature of the investigator or his representative obtaining consent:

Name_____signature_____Date_____

_____

Name and signature of the investigator or his representative obtaining consent:

Name_____signature_____Date_____

NOTE:-

For observational studies in nature or those in which only patient's tissue, body fluids are collected for any kind of analysis the following elements in the patient information leaflet will need be included – background of the study the purpose for which the sample will be used: confidentially of data are right to refuse to give specimens should be included.

Points 6, 7,8,9,10,11 of consent document may be excluded in such cases.

ஆராய்ச்சி ஒப்புதல் கடிதம்

ஆராய்ச்சி தலைப்பு:

செங்கல்பட்டு அரசு பொது மருத்துவமனையில் தோல் சிகிச்சைப்பிரிவில் அரிக்கும் தடிப்புகள் கொண்ட தோல் நோய்க்கு வழங்கப்படும் செட்ரிசின், மான்டிலுக்காஸ்ட், ரேனிட்டிடின் ஆகிய மருந்துகளின் பயன்பாடு மற்றும் பாதுக்காப்பு குறித்ததான ஒப்பீட்டு ஆய்வு.

திரு/திருமதி _____

_____

என்ற விலாசத்தில் வசிக்கும் நான், எனக்கு அளிக்கப்பட்ட தகவல் படிவத்தில் உள்ள விஷயங்களைப் படித்தும் கேட்டும் புரிந்து கொண்டேன்.

இந்த ஆய்விற்குத் தேவையான இரத்தப் பரிசோதனைகளுக்கு உட்பட சம்மதிக்கிறேன்.

இந்த ஆராய்ச்சியில் பிறரின் நிர்ப்பந்தமின்றி என் சொந்த விருப்பத்தின் பேரில் நான் பங்கு பெறுகிறேன்.

ஆய்வில் தொடர்ந்து பங்குபெற விருப்பம் இல்லை என்றால் விலகிக் கொள்ளலாம் என்றும் அறிந்து கொண்டேன்.

ஆய்வின் முடிவினை சொந்த அடையாளங்களை வெளியிடாமல் மருத்துவ ஆராய்ச்சிக்காக பயன்படுத்திக் கொள்ள சம்மதிக்கிறேன்.

நாள்:

இடம்: கையொப்பம்

Information to participants

Principal Investigator:- Dr.S. SWEETLIN
MD Pharmacology Postgraduate
Chengalpattu Medical College
Chengalpattu.

Name of the participant:

Title : **"A prospective, randomized, open label, comparative study of montelukast and ranitidine as an add on therapy to cetirizine in chronic urticaria"**

This study is conducted in our institution, Chengalpattu Medical College/Hospital, Chengalpattu.

You are invited to take part in this study. The information in this document is meant to help you to decide whether or not to take part. Please feel free to ask if you have any queries or concerns.

You are being asked to participate in this study conducted in the department of Dermatology and department of Pharmacology, Chengalpattu Medical College.

Purpose of research :

To compare the efficacy and safety of combination therapy of Montelukast and Ranitidine as an add on therapy to Cetirizine in chronic urticaria.

The study is conducted with permission from the Institutional ethical committee.

Study design : Randomized prospective, open labeled comparative study.

Study Procedure

Patients who fulfilled the selection criteria will be recruited for the study. After getting informed consent, patients will be randomly allotted to either group A (cetirizine+montelukast) or group B (cetirizine +ranitidine). Complete history, clinical examination, Urticaria Activity Score7 (UAS7) assessment and baseline laboratory investigations will be taken at the beginning of the study.

Patient will be educated to keep daily record of urticaria activity score. Review of patient's record and clinical examinations of patients according to the Urticaria Activity Score7 (UAS7) will be done. Sum of score will be calculated at the end of every week for 4 weeks. Baseline laboratory investigations will be repeated at the end of fourth week. Patient will be followed up for 2 weeks after completion of the study.

In addition, if you notice any physical, you must contact the persons listed at the end of the document.

You may have to come to hospital for examination and investigations apart from your scheduled visits if require

You must not participate if you are pregnant, breast feeding a child or suffering from any serious medical illness like kidney or liver disease, cancer or any surgical illness.

Benefits of the study :

The results of the research may provide benefits to the society in term of thereauptic advancements and benefits future of chronic urticaria patient.

தகவல் படிவம்

செங்கல்பட்டு அரசு பொது மருத்துவமனையில் தோல் சிகிச்சைப்பிரிவில் அரிக்கும் தடிப்புகள் கொண்ட தோல் நோய்க்கு வழங்கப்படும் செட்ரிசின், மான்டிலுக்காஸ்ட், ரேனிட்டிடின் ஆகிய மருந்துகளின் பயன்பாடு மற்றும் பாதுக்காப்பு குறித்ததான ஒப்பீட்டு ஆய்வு மேற்கொள்ளப்படுகிறது.

- இந்த ஆய்வு அனுபவம் வாய்ந்த மருத்துவர்களின் உதவியோடு நடத்தப்படுகிறது.

- இம்மருந்துகள் அனுதின பயன்பாட்டில் உள்ள மருந்துகளே. இம்மருந்துகளினால் மிகப் பெரிய அளவில் பக்க விளைவுகள் ஏற்பட வாய்ப்புகள் இல்லை.

- ஆராய்ச்சியின் போது ஒரு பிரிவினருக்கு செட்ரிசின்னுடன் மான்டிலுக்காஸ்ட் மாத்திரையும் மற்றொரு பிரிவினருக்கு செட்ரிசின்னுடன் ரேனிட்டிடின் மாத்திரையும் வழங்கப்படும்.

- நோயாளிகள் இம்மருந்துகளை பயன்படுத்தியபின் நோயின் தன்மையை குறித்து வைக்கும் முறைகளில் பயிற்றுவிட்கப்படுவார்கள்.

- ஆராய்ச்சியின் தொடக்கத்திலும் முடிவிலும் இரத்தப் பரிசோதனை செய்யப்படும்.

- நோயின் தன்மைகளை வெளியிடும்போது தங்களது பெயரையோ அடையாளங்களையோ வெளியிட மாட்டோம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

- இந்த ஆராய்ச்சியில் பங்கேற்பது உங்களுடைய விருப்பத்தின் பேரில் தான் இருக்கிறது. மேலும் நீங்கள் எந்நேரமும் இந்த ஆராய்ச்சியிலிருந்து பின் வாங்கலாம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

- இந்த சிறப்பு பரிசோதனைகளின் முடிவுகளை ஆராய்ச்சியின் போது அல்லது ஆராய்ச்சியின் முடிவின்போது தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

நாள்:

இடம்: கையொப்பம்

INSTITUTIONAL ETHICS COMMITTEE

CHENGALPATTU MEDICAL COLLEGE , CHENGALPATTU

APPROVAL OF ETHICAL COMMITTEE

To

Dr. Sweetlin S,
1st Year PG student (Pharmacologoy),
Chengalpattu Medical College,
Chengalpattu

Dear Dr.

The Institutional Ethical Committee of Chengalpattu Medical College reviewed and discussed your application to conduct the clinical / dissertation work entitled

A PROSPECTIVE, RANDOMIZED, OPEN LABLE, COMPARATIVE STUDY OF MONTELUKAST AND RANITIDINE AS AN ADD ON THERAPY TO CETIRIZINE IN CHRONIC URTICARIA

ON 19.02.2015

The following documents reviewed

1. Trial protocol, dated _____version no
2. Patient information sheet and informed consent form in English and / or vernacular language.
3. Investigators Brochure, dated _____version
4. Principal Investigators current CV
5. Investigators undertaking

The following members of the Ethics committee were present at the meeting held on

Date 19.02.2015 Time 11.00 am Place Chengalpattu Medical College

Approved _____ Chairman Ethics Committee

_____ Member secretary of Ethics Committee.

Name of each member with designation:-

Clinical Members

1. Dr.K.Srinivasagalu MD.,
   Prof & HOD of Medicine, CHMC

2. Dr.C.Srinivasan MS.,
   Prof & HOD of Surgery, CHMC

Biological Scientist

3. Dr.K.Baskaran MD.,
   Asso Prof of Pharmacology, CHMC

Non Clinical Member

4. Dr.P.Parasakthi MD
   Prof & HOD of Forensic Medicine,CHMC

5. Member from Nongovernmental
   Voluntary Organisation : Mr.P.Durairaj

6. Philosopher : Mr.K.S.Ramprasad

7. Lawyer : Lr. I. M. Karimala Basha

8. Layperson : Mr.Dilli

We approve the clinical trial to be conducted in its presented form

The Institutional Ethics Committee expects to be informed about the progress of the study and any SAE occurring in the course of the study, any changes in protocol and patient information / informed consent and asks to provide copy of final report.

Yours sincerely

19/2/15

Member secretary, Ethics Committee

MASTER CHART

S. no	Age	Sex	UAS 1st week max=42	UAS 2nd week max=42	UAS 3rd week max=42	UAS 4th week max=42	TOTAL SCORE (max=168)	onset of urticaria (months)	eosinophil count			Hemoglobin			Total leucocyte count			ESR			Platelet count			blood urea			Serum Creatinine			SGOT			SGPT		
1	26	F	25	18	7	0	50	6	9	3	5	10	11	12.6	7734	7700	6955	12	12	8.5	3	3	2.06	21	20	23	1	1	1	12	16	12	17	16	15
2	55	F	28	18	10	2	58	12	8	4	4	9.7	9.8	10.4	8800	9000	7652	13	11.5	11	2.6	2.3	2.12	20	22	20	0.72	0.72	0.62	15	13	14	17	22	16
3	23	M	22	14	0	0	36	3	2	6	6	11.2	10.7	9.6	8750	7700	6862	11	11.5	10	2.54	2.45	2.14	21	23	22	0.62	0.73	0.63	13	16	12	16	18	13
4	32	F	35	25	16	10	86	12	8	7	7	9	8.8	11.5	7805	7580	7798	13	12	10	2.1	2.6	2.56	21	20	22	0.63	0.69	0.8	18	16	11	13	17	18
5	34	F	18	7	0	0	25	10	9	8	8	9.4	8.9	10.2	7830	7568	5791	12	12.5	12.5	2.5	2.4	2.75	22	24	23	0.7	0.78	0.76	20	14	15	19	15	20
6	53	M	23	9	2	0	34	24	8	10	10	8.3	9.2	12	6786	6950	6700	10	10	11	2.8	2.14	2.14	21	22	21	0.76	0.64	0.74	21	15	13	15	16	21
7	48	M	21	16	7	0	44	4	12	11	6	10.5	10.5	9.5	6500	6450	6587	9	9.5	9.5	2.56	2.4	2.99	20	22	24	0.65	0.77	0.76	15	13	14	17	14	15
8	32	F	20	10	0	0	30	6	8	10	10	9.8	9.6	9.3	6600	6300	5865	10	8	13	2.5	2	2.68	24	20	20	0.71	0.79	0.76	16	16	17	16	19	16
9	58	F	15	7	7	3	32	10	9	5	8	9.5	9.6	9.4	8562	9020	5865	9.5	9	9.5	2.8	2.5	2.34	21	20	23	0.72	0.62	0.71	12	18	16	15	19	12
10	26	F	14	6	3	0	23	3	4	6	9	9.2	9.4	10.4	7753	7522	6860	9.5	10	12.5	2.3	3.24	2.15	25	22	25	0.73	0.69	0.79	13	15	14	18	17	13
11	53	F	18	12	10	3	43	24	9	8	8	10.2	10.5	10.6	6862	6800	6800	12.5	12	11.5	2.55	2.6	2.6	23	21	21	0.69	0.73	0.77	13	16	16	16	16	13
12	27	M	22	7	0	0	29	3	7	7	9	13	11.9	12.3	5845	5750	6796	8.5	8.8	10	2.14	2.15	2.4	25	22	23	0.78	0.81	0.72	15	13	12	22	13	15
13	30	F	18	9	3	0	30	6	9	4	7	10.4	11.1	12.4	6623	6700	5867	11	11	8	2.56	2.67	3.5	21	23	22	0.64	0.73	0.73	14	16	13	18	19	17
14	38	F	15	6	0	0	21	5	10	6	9	10.2	10.6	11	7862	7600	5863	10	9.5	9.5	2.6	2.85	2.4	22	20	24	0.77	0.75	0.69	10	12	14	17	15	15
15	33	M	16	11	0	0	27	10	8	7	9	11.3	11.7	11.6	8739	8900	6752	10	9	11	2.65	2.8	2.9	21	23	21	0.79	0.69	0.78	17	14	18	15	17	16
16	44	F	17	10	4	4	35	18	8	4	4	10	9.9	11	6845	6450	6200	12.5	12	12	2.5	2.3	3.12	20	22	20	0.62	0.75	0.64	18	13	11	16	15	14
17	46	F	23	18	10	4	55	18	9	8	12	8.2	9.1	12	6955	6500	6045	11	11.5	11	2.8	2.56	2.35	25	23	23	0.69	0.8	0.79	16	18	12	14	16	19
18	51	F	15	6	0	0	21	4	1	9	10	7	8.1	11.3	7652	6960	6235	10	10	11	2.5	2.4	2.46	20	22	27	0.73	0.82	0.65	15	10	16	20	16	19
19	54	F	13	4	0	0	17	7	7	9	9	8.9	10	10.6	6862	6540	6240	10	9	11.4	2.65	2.35	2.55	21	21	22	0.79	0.72	0.78	14	12	17	19	15	18
20	40	F	25	16	16	9	66	12	8	5	1	9.8	10.1	10.7	7798	7950	5800	9.5	10	10.2	2.56	2.45	2.01	22	20	20	0.7	0.62	0.73	17	14	12	17	13	15
21	43	M	14	10	7	3	34	10	8	7	7	10.2	9.8	11.6	5791	6021	6980	9.5	9.5	10.5	3.45	2.12	2.09	21	23	20	0.66	0.63	0.82	12	15	11	19	21	16
22	20	F	19	10	7	3	39	6	8	8	8	10	9.8	8.9	6700	6750	6865	13	13	9.5	2	2.84	2.35	22	21	22	0.74	0.7	0.71	15	16	15	16	15	17
23	51	M	20	9	4	0	33	3	9	3	10	12.4	12.6	11.4	6587	6860	6100	8.4	9.5	9	2.25	2.5	2.98	20	20	21	0.73	0.76	0.76	14	16	13	18	16	15
24	32	F	17	11	5	5	38	9	7	8	8	10.4	10.4	8.8	5865	5682	6560	14	12.5	9	2.01	2.45	2.42	22	24	22	0.79	0.62	0.74	16	15	14	15	15	13
25	37	F	19	11	3	0	33	12	8	10	8	11	10.6	8.9	6860	6952	7500	11	11.5	10.6	2.15	2.56	2.65	20	25	20	0.81	0.69	0.76	14	13	15	16	16	16
26	22	M	23	18	14	10	65	12	9	9	9	11.6	11.8	9.2	6800	6320	6950	9.6	10	10.8	2.86	2.58	2.65	21	23	24	0.73	0.73	0.62	12	14	16	17	17	19
27	44	M	21	9	9	4	43	6	10	8	4	11	11.5	10.5	6796	9862	6560	8.6	8	13.5	2.15	2.06	2.45	22	20	21	0.75	0.79	0.73	17	16	16	16	15	15
28	43	M	15	8	3	0	26	3	6	11	6	12	11.9	9.6	5867	5462	7500	9	9.5	9	2.3	2.12	2.54	24	20	20	0.69	0.7	0.75	16	14	18	15	13	16
29	45	F	12	3	0	0	15	3	5	8	12	11.3	11	11.3	5863	4963	6950	12	11	9.8	2.65	2.14	2.25	21	24	21	0.75	0.66	0.69	15	16	16	16	16	14
30	55	F	11	7	3	0	21	5	11	5	9	10.6	10.8	9.9	6752	5652	6560	13.5	12	8	2.45	2.56	2.5	22	22	22	0.8	0.74	0.75	14	15	16	14	19	17
31	53	F	15	4	0	0	19	6	8	8	8	10.7	10.4	10	7766	7568	6800	11.4	11	12.5	2.45	2.75	2.8	24	20	21	0.82	0.62	0.63	13	16	14	15	15	15

S. no	Age	Sex	UAS 1st week max=42	UAS 2nd week max=42	UAS 3rd week max=42	UAS 4th week max=42	TOTAL SCORE (max=168)	onset of urticaria (months)	eosinophil count			Hemoglobin			Total leucocyte count			ESR			Platelet count			blood urea			Serum Creatinine			SGOT			SGPT		
32	41	F	19	10	7	4	40	6	9	9	8	10	10.3	10.1	6893	6954	6450	11	11	12	3.12	2.14	2.56	21	22	20	0.72	0.69	0.82	14	13	15	16	16	16
33	21	F	23	14	9	0	46	10	8	8	9	9.8	9.6	11.6	5807	5623	6250	10.5	11.5	15	2.35	2.99	2.5	20	23	24	0.76	0.73	0.72	15	16	13	13	14	14
34	29	F	26	13	5	5	49	12	7	12	4	9.6	9.5	8.9	5769	5821	6200	9.5	9	11	2.46	2.68	2.8	23	25	21	0.74	0.79	0.76	16	15	16	21	12	19
35	29	M	22	10	4	0	36	9	6	9	10	11.3	10.4	11.4	6651	6620	6045	9	9.5	9	2.55	2.34	2.3	27	24	25	0.76	0.7	0.71	13	16	18	15	13	19
36	31	F	17	5	0	0	22	7	9	8	3	9.9	9.5	8.1	5862	6600	6235	9	9	10	3.05	3.4	2.55	21	20	23	0.73	0.66	0.79	17	12	15	16	17	20
37	39	F	13	6	0	0	19	3	4	8	8	10	10.4	10	5459	6320	6240	10.6	10	9.5	2.09	2.45	2.66	22	23	25	0.73	0.74	0.62	12	11	14	17	19	21
38	32	F	18	7	0	0	25	6	8	9	9	10.1	10	10.1	6596	6564	5800	11.2	11	13	2.35	2.49	2.56	20	22	21	0.79	0.76	0.63	14	13	17	15	12	15
39	40	F	16	11	11	7	45	12	7	4	8	11.2	11.8	9.8	6359	6500	6980	13.5	12	9.5	2.98	2	2.5	21	22	22	0.74	0.74	0.81	13	14	16	13	18	16
40	39	M	16	11	7	0	34	7	4	8	8	11.7	11.6	9.8	7755	7452	5866	9	9.5	12.5	2.42	3	2.3	24	22	21	0.76	0.78	0.76	15	12	14	16	20	12
41	36	F	15	11	11	7	44	4	12	9	2	8.5	8.9	12.6	6869	7420	6854	9.8	10	11.5	2.65	3.22	2.45	20	23	20	0.74	0.72	0.75	16	11	15	19	21	13
42	53	M	21	7	0	0	28	3	9	8	10	11	11.4	10.4	6878	5620	9786	8	9.5	10	2.65	2.66	2.35	20	21	21	0.76	0.77	0.69	14	15	12	15	13	16
43	31	F	24	14	9	3	50	18	8	9	9	9.6	9.5	11.6	5792	6200	6635	12.5	11	8	2.45	2.56	2.56	23	24	21	0.82	0.76	0.75	12	13	13	16	15	19
44	19	M	12	10	3	0	25	5	8	7	8	12.1	11.9	11	6700	6045	5862	12	10	9.5	2.54	2.5	2.35	22	20	22	0.77	0.72	0.8	15	14	10	14	16	15
45	23	F	16	7	0	0	23	6	9	9	4	9.8	10.3	12	6635	6235	5459	15	14	11	2.25	2.3	2.4	23	21	21	0.74	0.71	0.64	16	15	18	12	17	17
46	32	F	17	8	8	4	37	4	4	9	9	9.4	9.8	11.3	6805	6240	6596	11	12	12	2.5	2.45	2.13	20	22	20	0.75	0.81	0.72	13	16	11	13	19	18
47	46	F	20	7	4	0	31	10	10	3	7	9.9	9.4	10.6	5813	5800	6500	10	11.5	11	2.29	2.35	2.68	23	23	20	0.72	0.74	0.62	16	13	12	16	15	21
48	48	F	19	4	0	0	23	2	3	12	9	10.2	11	10.7	7440	6980	6600	9.5	9.5	11	2.54	2.56	2.34	24	20	21	0.76	0.77	0.69	16	14	13	14	15	16
49	25	M	16	7	0	0	23	6	8	10	10	13	12.6	9.6	6965	7503	8562	7.5	8	11.5	2.23	2.35	3.01	23	22	22	0.74	0.73	0.64	14	15	15	18	16	18
50	24	F	13	9	5	0	27	9	8	8	8	10.8	10.4	11.3	5698	5632	7753	12	11.5	9	2.09	2	2.15	20	20	21	0.76	0.71	0.77	15	16	14	12	12	19
51	19	F	30	23	20	18	91	12	9	9	8	9.6	9.6	9.9	6835	6855	6862	9.5	9.5	9.5	2.3	2.56	2.02	22	21	22	0.73	0.77	0.79	13	13	10	22	15	15
52	34	M	29	23	18	7	77	6	8	4	9	11.3	11.5	11.2	6685	7000	5845	13	12.5	9	2.65	2.25	2.3	22	24	20	0.73	0.76	0.62	12	17	17	18	16	15
53	39	F	33	24	16	10	83	18	9	6	6	9.9	10.2	11.3	5866	6020	6623	8.4	9	11	2.45	2.64	2.55	23	26	23	0.79	0.74	0.63	14	20	18	16	17	13
54	44	M	28	31	22	17	98	12	7	9	6	11.2	12	10	6854	6505	8210	12	11	10	2.45	2.66	2.14	21	24	22	0.74	0.76	0.64	11	16	16	17	16	16
55	48	F	18	9	0	0	27	6	9	1	8	10.5	9.5	8.2	9786	8450	7400	13.5	12	13.5	2.48	2.56	2.34	24	22	23	0.76	0.72	0.76	14	15	15	23	13	19
56	50	F	21	11	10	10	52	9	9	9	9	9.8	9.3	7	6635	6245	6235	11.4	12	12.5	2.35	2.5	2.56	20	22	25	0.74	0.77	0.71	15	14	14	20	19	15
57	53	F	28	12	3	0	43	3	3	8	8	9.5	9.4	8.9	7789	6865	5954	11	12.5	12	2.46	2.3	2.1	21	20	22	0.76	0.74	0.79	16	16	15	16	15	16
58	34	F	24	24	11	10	69	18	12	8	9	9.2	10.4	9.8	5762	6100	6025	10.5	9.5	11.5	2.55	2.45	2.5	25	20	22	0.82	0.75	0.71	15	14	14	15	17	14
59	58	F	34	30	25	15	104	12	10	8	7	10.2	10.6	10.2	6856	6560	5896	9.5	10	11	3.05	2.35	2.8	20	23	20	0.77	0.72	0.68	16	15	16	18	18	18
60	40	M	31	17	10	5	63	6	7	6	9	11	12.3	10	8869	7500	6010	9.6	9	10	2.63	2.56	2.56	22	27	20	0.74	0.76	0.69	13	16	16	19	21	15
61	18	M	22	23	20	16	81	7	8	8	9	12	12.4	12.4	6860	6950	7450	8.6	8	11.5	2.35	2.35	2.5	23	21	22	0.72	0.73	0.78	17	16	15	14	16	16
62	21	M	29	26	21	10	86	4	9	7	3	10.8	10.5	10.4	6758	6560	6350	9	8.5	10.5	1.95	2.4	2.5	20	22	21	0.7	0.73	0.64	12	13	14	15	18	17
63	25	F	36	22	12	7	77	3	4	4	12	9	8.3	11	6790	6800	7200	12	11.5	9.5	2.78	2.99	2.3	24	20	24	0.72	0.79	0.77	18	14	13	16	19	19
64	33	M	32	14	12	6	64	4	6	9	10	11.6	11.3	11.6	6000	6450	5862	9	9	10	2.66	2.68	2.45	22	21	23	0.77	0.74	0.79	16	11	14	13	15	16
65	38	F	17	10	4	0	31	6	10	7	9	10.8	10.4	11	6025	6250	5698	9	9.5	11	2.42	2.34	2.35	22	24	20	0.76	0.76	0.62	15	14	15	18	14	21

S. no	Age	Sex	UAS 1st week max=42	UAS 2nd week max=42	UAS 3rd week max=42	UAS 4th week max=42	TOTAL SCORE (max=168)	onset of urticaria (months)	eosinophil count			Hemoglobin			Total leucocyte count			ESR			Platelet count			blood urea			Serum Creatinine			SGOT			SGPT		
66	41	F	37	15	7	3	62	9	7	9	10	9.6	10	12	6680	6500	5421	10.6	12	15	2.65	3.4	2.56	20	20	22	0.72	0.74	0.63	15	16	14	20	19	19
67	58	F	23	20	19	11	73	9	9	10	7	11.3	11.4	10.6	7850	7500	7805	11.2	10.5	9.5	2.65	2.45	2.35	20	22	21	0.71	0.71	0.72	16	15	16	21	20	18
68	36	F	35	31	29	15	110	10	8	8	9	9.9	9.3	12.3	6568	6500	7830	13.5	12.5	8	2.45	2.49	2.03	22	24	20	0.73	0.72	0.77	13	13	15	15	15	17
69	40	F	21	17	16	10	64	12	11	9	8	10.8	10.4	12.4	6803	6850	6786	12	11	7.5	2.54	2	2.65	21	23	21	0.78	0.73	0.76	17	19	14	16	18	21
70	19	F	13	7	2	0	22	7	9	8	8	9.6	10	10.5	8960	7500	6500	11	10	9.8	2.25	2.5	2.45	22	20	22	0.73	0.69	0.72	16	12	18	12	17	16
71	22	M	32	19	15	11	77	9	9	9	6	11.3	11.1	8.3	6862	6425	6600	8.5	7	10	2.5	2.8	2.4	22	22	21	0.82	0.78	0.71	13	13	17	13	18	18
72	27	F	29	21	11	9	70	6	7	7	9	9.9	10.2	10.1	7861	7600	8562	12.5	11	15	2.29	2.23	3.5	20	21	20	0.71	0.64	0.81	15	14	16	13	15	19
73	32	M	31	12	10	0	53	4	8	9	4	11.2	10.5	11	7798	7596	7753	10	11	11	2.85	2.36	2.4	23	24	24	0.76	0.77	0.74	17	16	14	15	18	18
74	41	M	38	25	18	12	93	10	7	9	9	10.5	11	11.3	8960	8450	5862	9	9	10	3	2.56	2.9	22	20	23	0.77	0.79	0.77	16	14	12	14	14	17
75	21	M	36	12	6	0	54	12	9	5	8	9.8	10	9.9	7932	7650	5459	10	10.5	9.5	2.5	2.12	2.5	23	20	21	0.72	0.62	0.73	15	16	12	10	12	21
76	58	F	26	17	13	12	68	18	13	6	11	9.5	9.5	10.8	6521	6800	6596	11	11	8.6	2.29	2.65	3.24	22	23	25	0.73	0.7	0.71	13	14	12	16	13	10
77	55	F	16	13	6	1	36	6	9	8	10	8.3	8.6	9.6	6508	6425	6458	15	13.5	9	2.04	2.02	3.02	21	22	23	0.69	0.75	0.64	16	12	11	16	16	16
78	19	M	23	16	7	3	49	3	5	9	9	10.9	11.3	11.3	7005	6825	6786	9.5	9	12	2.23	2.36	2.5	20	23	25	0.78	0.72	0.77	19	12	15	19	19	16
79	30	M	30	17	13	10	70	2	6	4	7	11.1	11.4	9.9	6522	6450	6500	8	9	9	2.09	2.55	2.8	23	23	21	0.64	0.77	0.79	13	10	13	18	15	19
80	45	M	30	25	20	11	86	9	8	12	8	11.5	11.4	10.5	6545	6820	6600	7.5	8	9	2.98	2.12	2.56	20	24	22	0.77	0.76	0.62	18	16	14	19	16	22
81	50	M	34	23	17	10	84	6	2	9	8	9.9	9.4	9.8	6021	6920	8562	9.8	8	10.6	2.14	2.5	2.5	21	23	21	0.72	0.72	0.72	20	18	15	19	14	13
82	20	M	22	17	8	4	51	7	4	8	5	9	10	9.9	7102	6895	7753	10	8.5	11.2	2.5	2.36	2.5	22	20	20	0.76	0.71	0.77	21	11	16	15	18	16
83	29	F	27	23	20	9	79	6	6	8	2	9.4	9.7	11	6720	6456	6862	15	13.8	13.5	2.8	2.01	2.3	24	21	25	0.63	0.73	0.74	15	11	16	16	12	14
84	38	F	40	29	20	13	102	18	7	9	9	8.3	9.2	9	6800	6765	5845	11	11.5	9.5	2.3	2.15	2.45	21	20	20	0.7	0.74	0.75	16	12	15	20	19	16
85	30	F	35	30	28	11	104	12	8	4	6	10.5	9.8	12	6750	6720	6623	10	9	12	2.55	2.12	2.35	22	21	21	0.76	0.73	0.62	12	15	16	22	20	12
86	28	F	25	33	30	26	114	16	10	10	7	9.8	9.4	8.3	6400	5965	6540	9.5	9	11	2.14	2.3	2.56	23	22	22	0.65	0.78	0.69	13	14	13	13	21	13
87	36	F	3	16	17	15	51	7	1	3	8	9.5	8.9	9.4	5862	5600	7950	10.5	9	10.5	2.34	3.2	2.35	20	21	21	0.71	0.73	0.73	13	13	16	16	18	16
88	47	F	38	13	9	0	60	6	10	8	10	9.2	10.5	9.6	6586	6685	6021	11	9	10	2.56	2.6	2.48	22	20	22	0.72	0.82	0.79	15	18	15	14	17	16
89	53	F	27	13	9	5	54	3	4	9	2	10.2	9.8	11.3	6542	6400	6750	12	11	9	2.1	2.4	2.35	20	24	23	0.73	0.71	0.7	14	14	16	18	15	21
90	19	M	28	14	11	5	58	2	8	4	10	11	9.9	9.9	5478	5500	6860	9	10	11	2.5	3.5	2.46	22	21	20	0.69	0.76	0.66	10	15	17	23	19	19
91	31	F	25	17	12	12	66	8	9	9	8	9	9.2	11.2	7452	7900	7543	14	13.5	12	2.8	2.4	2.55	23	25	22	0.78	0.77	0.74	17	14	16	15	18	18
92	29	M	30	32	21	9	92	9	10	8	8	12	11.2	8.6	7582	7600	6800	10	12.5	12	2.56	2.9	3.05	20	23	22	0.64	0.76	0.73	16	16	15	19	16	17
93	29	F	29	20	12	0	61	11	12	7	2	8.3	9.3	9.4	7003	6800	6425	13	12	12.5	2.5	2.5	2.03	24	25	23	0.77	0.73	0.79	14	15	14	16	16	23