

Efficacy of Montelukast as Added Therapy in Patients with Chronic Idiopathic Urticaria

Sujoy Khan^{*,1} and Nuala Lynch^{1,2}

¹Department of Immunology, Frimley Park Hospital NHS Foundation Trust, Portsmouth Road, Frimley, Surrey, GU16 7UJ, UK

²Hook Surgery, Reading Road, Hook, Hampshire, RG27 9ED, UK

Abstract: Chronic idiopathic urticaria is a common skin disorder characterized by recurrent appearance of wheals and/or angioedema for more than 6 weeks without an identifiable cause. Consensus guidelines suggest use of leukotriene receptor antagonists (montelukast or zafirlukast) in patients whose urticaria is resistant to antihistamines. Our objectives were (1) document the efficacy of montelukast in our patients, and (2) evaluate whether any clinical features or available laboratory investigations were associated with a response to montelukast.

Patients who received montelukast between the years 2008-2011 (4-year period) were retrospectively identified from clinic letters. Clinical features and laboratory investigations were collected and analyzed. The primary end point was adequate control of disease without the need for systemic steroid therapy.

25 patients (10 males and 15 females; median age, 33 years; age range, 13-66 years) with an average duration of urticaria at 3.8 years received montelukast 10mg daily. 12 patients (48%) were better on montelukast with combined anti-H1 and anti-H2 therapy, with no statistical significance between median age and duration of urticaria between males and females. In 11 patients, montelukast had no effect and in 2 patients the urticaria worsened after montelukast was started. 15 patients had peripheral blood basopenia of which 5 patients responded to montelukast. Two patients had positive antinuclear antibody, 3 thyroid peroxidase antibodies and 4 with positive basophil histamine release. All 20 patients who had complement C3 and C4 levels done were within normal limits. Four of 6 patients (67%) with positive specific IgE responded to montelukast and combined anti-H1/H2 therapy.

Almost half of our patients with chronic urticaria responded to montelukast and combined anti-H1 and anti-H2 therapy. We were unable to identify any clinical features or laboratory markers that were associated with a response to montelukast. Further studies are required to understand the failure of response of leukotriene inhibition in urticaria.

Keywords: Antihistamine, chronic idiopathic urticaria, leukotriene, montelukast.

INTRODUCTION

The EAACI/GA²LEN/EDF/WAO consensus guidelines for the diagnosis and management of urticaria published in 2009 was based on expert recommendations from the Third International Consensus Meeting on Urticaria (Urticaria 2008), joint initiative of the EAACI Dermatology Section, Global Allergy and Asthma European Network (GA²LEN), European Dermatology Forum (EDF) and World Allergy Organization [1, 2] and highlighted the absence of reliable assessment tools (mainly laboratory markers) and effective treatments for this common condition. A subsequent update from the GA²LEN task force also identified several unmet clinical needs in patients with chronic spontaneous urticaria [3]. It is estimated that up to 1% of the population suffers from chronic urticaria (CU) and that all age groups are affected although the peak incidence is between 20 and 40 years of age. In most cases the disease lasts between 1-5 years, but the duration can be longer in those with severe urticaria, those with concurrent angioedema, and in those with the physical component (including a positive

autologous serum skin test). Urticaria is characterized by itchy, red, raised (wheal) and flare skin reactions that lasts usually a few hours (typically <24 hours) and is classified as chronic if it lasts >6 weeks. The chronic spontaneous form of urticaria does not need any stimulus and referred to as chronic idiopathic urticaria (CIU) [1-3].

The pathogenesis of CU is complex as illustrated in Fig. (1). Up to half of patients with CIU have an IgG autoantibody directed against the alpha subunit of the high-affinity IgE receptor (FcεR1α) which is the concept of autoimmune urticaria [4-6] that leads to persistent cutaneous mast cell and basophil activation (Fig. 1). The roles of the coagulation cascade and fibrinolysis activation [7], including several cytokines [8-21] and the yet elusive soluble serum factor that leads to release of histamine from basophils which has been the basis of the serum-induced basophil histamine release assay (described in detail in the 'Methods' section [22, 23]). Although histamine plays a significant role in diseases like CU and eczema, prostaglandins, leukotrienes (LTs) and cytokines prolong the inflammatory process and hence leukotriene receptor antagonists (LTRAs) may well modulate the underlying abnormalities and lead to remission of urticaria.

The consensus guidelines have adopted the management of urticaria into (1) avoidance measures and (2)

*Address correspondence to this author at the Department of Immunology, Frimley Park Hospital NHS Foundation Trust, Frimley, Surrey, GU16 7UJ, UK; Tel: +44 (0) 1276-604118; Fax: +44 (0) 1276-604360; E-mail: sujoykhan@gmail.com

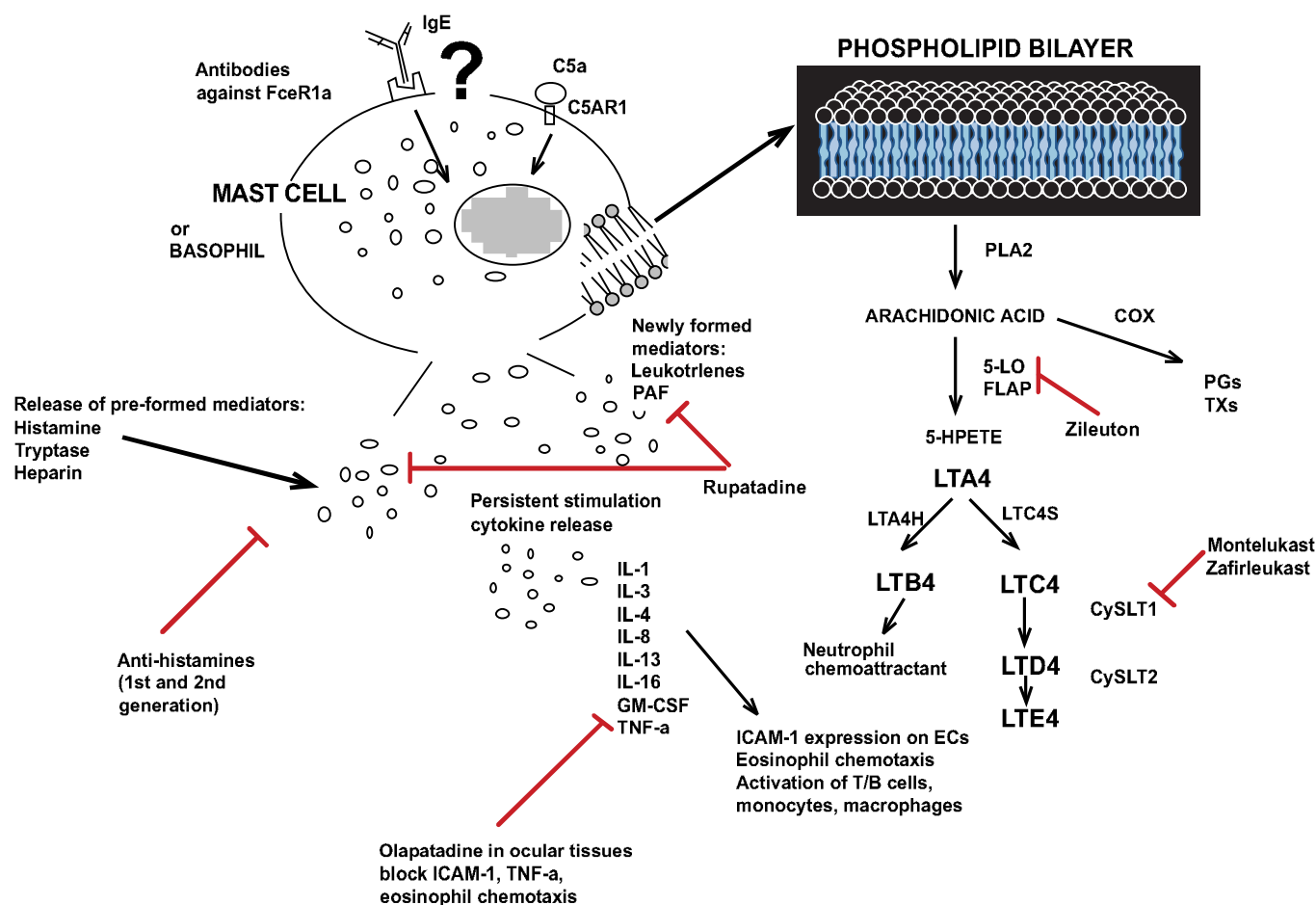


Fig. (1). Mediators of itch and inflammation in urticaria and some of the therapeutic agents available.

pharmacotherapy – nonspecific and specific. The avoidance approach outlines elimination or treatment of eliciting stimulus or cause (such as NSAID-induced urticaria/angioedema, physical causes, treatment of an infectious trigger etc) that is not possible in all cases (i.e., those with CIU). The second approach is lowering or inhibiting mast cell mediator release and the most commonly used non-specific drugs that inhibit mast cell release are corticosteroids. Specific treatment approaches involves use of non-sedating long-acting antihistamine (anti-H1) drugs such as cetirizine, levocetirizine, loratadine, desloratadine and fexofenadine provide both anti-allergic and anti-inflammatory effects such as inhibition of cytokines release from basophils and mast cells as well as reduction of chemotactic activity of eosinophils (Fig. 1). Other treatment options that have significant activity on mediator release on basophils include the calcineurin inhibitor cyclosporin A [24-32], and occasionally ultraviolet therapy [33-37].

Montelukast is an orally active LTRA licensed for the maintenance treatment of asthma (GINA Step 4) and to relieve symptoms of seasonal allergies. Montelukast binds to and blocks the action of leukotriene D4 (LTD4) on the cysteinyl-leukotriene receptor CysLT1 in the lungs, with almost no interaction with other anti-allergy drugs (Table 1, Fig. 2). This reduces the bronchoconstrictive and inflamma-

tory effects of LTD4 in the airways and therefore not useful for the treatment of acute asthma attacks. LTs such as LTC4, LTD4 and LTE4 have important roles in the pathophysiologic mechanisms of allergic inflammation after binding to activating receptors, cystenyl-LT1 (CysLT1) receptor and Cys-LT2 receptor [38-43]. Hence, LTRAs such as montelukast 10mg once daily or zafirlukast 20mg twice daily have been employed either as monotherapy or in combination with H1-receptor and/or H2-receptor antagonists, to treat different forms of CU, including cold urticaria, urticaria related to food additives, chronic autoimmune urticaria, steroid-dependent urticaria, delayed-pressure urticaria, CIU and dermatographism with varying results [44-50].

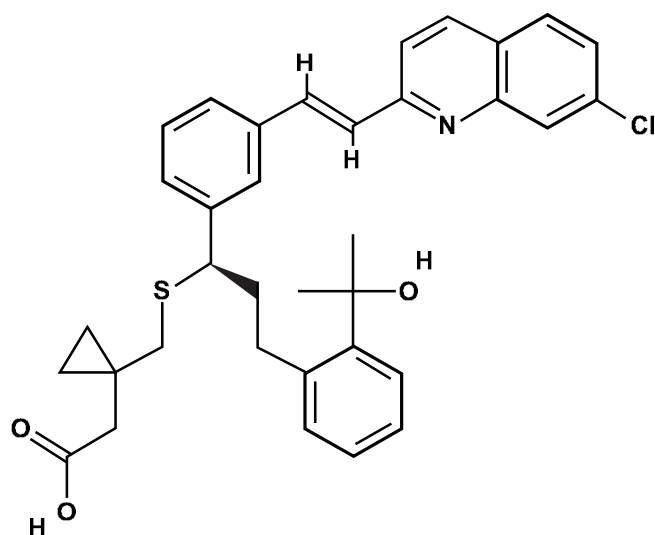
Data from few systematic clinical trials or case series suggest that a few patients with chronic and resistant idiopathic urticaria respond to leukotriene inhibition, but laboratory markers are still unavailable that would help the clinician identify which patients are likely to have a favourable response to montelukast [3]. It has been suggested that urticaria activity score (UAS, combination of wheal numbers and intensity of pruritis) be used to monitor effectiveness of therapy, but no reliable biomarkers are currently available to monitor the disease activity. Studies have also reported on the limited efficacy of the UAS and

Table 1. Overview of the Pharmacological and Side Effect Profile of Montelukast

Parameter	Pharmacological Profile
Mechanism of action	Orally active CySLTR1/LTD ₄ antagonist
Pharmacokinetics	Single Daily Dose 4mg/5mg (children); 10mg (adults)
C _{max} (ng/ml)	4mg granules (fasting): Geometric Mean±SD 198.8±53.8 Chewable tablets (fasting): GM±SD 201.7±91.6**
t _{max} (h)	5mg: 2h (fasting) 10mg: 3h (fasting)
AUC _{0-∞} (ng/ml/h)	4mg granules (fasting): GM±SD 1,223.1±342.3 Chewable tablets (fasting): GM±SD 1,208.3±467.4**
Effect of food intake	5mg chewable tablet: Mean oral bioavailability 73% (fasting) lowered to 63% by a standard meal
Protein binding	>99% protein bound
Metabolism	Metabolized by cytochrome P450 (CYP) 3A4 and 2C9
Elimination	Eliminated by the biliary route Plasma clearance averages at 45 ml/min (healthy adults)
Effect of age	Dosage adjustment not necessary in the elderly or in those with mild to moderate hepatic insufficiency or renal insufficiency
Side effect profile	Very common (≥1 in 10): upper respiratory infection (similar to placebo in clinical trials) Common (≥1 in 100 to <1 in 10): GI – diarrhoea, nausea, vomiting; skin – rash; hepatobiliary: elevated serum transaminases (ALT, AST); general: pyrexia (this adverse reaction was similar to placebo in clinical trials) Uncommon (≥1 in 1000 to <1 in 100): hypersensitivity reactions including anaphylaxis; asthenia, fatigue, malaise; dream abnormalities including aggressive behaviour among other psychiatric disorders; dizziness, paresthesias; dry mouth, dyspepsia; bruising, urticaria, pruritis Rare (≥1 in 10,000 to <1 in 1000): angioedema, palpitations, tremor, increased bleeding tendency Very rare (≥1 in 100,000 to <1 in 10,000): possible unmasking of Churg-Strauss syndrome, hallucinations with suicidality, erythema nodosum, hepatitis including eosinophilic hepatitis

Source: http://www.medicines.org.uk/emc/medicine/17718#PHARMACODYNAMIC_PROPS (Accessed 22, December, 2011)

Reference: Knorr *et al. Arch. Drug Info.*, **2010, 3, 37-43.



Ref: PubChem Public Chemical Database
Properties

Molecular Weight: 586.18324 [g/mol]

Molecular Formula: C₃₅H₃₆ClNO₃S

H-Bond Donor: 2

H-Bond Acceptor: 4

<http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=5281040>

(accessed 20, December, 2011)

Fig. (2). Structure of montelukast.

patient reported effectiveness of drugs or non recourse to corticosteroid therapy has been used as a measure of effectiveness of the treatment regime that resulted in complete remission of the urticaria [51, 52].

The objectives of this retrospective study were: (1) to document the efficacy of montelukast as added therapy in our patients, and (2) evaluate whether any clinical features or available laboratory investigations were associated with a response to montelukast.

METHODS

Patients who received montelukast between the years 2008-2011 (4-year period) were retrospectively identified from clinic letters. Clinical features of duration of urticaria, concomitant medication use, autoimmune features or existing organ-specific autoimmunity were recorded. Patients who required frequent pulsed courses of corticosteroids or on immunosuppressive agents to control the urticaria were excluded from the study.

Laboratory investigations such as the full blood count (including automated 5-part differential count for basophil counts [Coulter Gen. S], complement C3 and C4 levels, autoimmune serology (antinuclear antibody, organ-specific autoimmunity on rat liver kidney stomach tissue), specific IgE tests (ImmunoCAP250, Phadia) for standard aero-allergens and food allergens (if identified on history-taking), including the results of the serum-induced basophil histamine releasing assay were collected and analyzed. For this serum-induced basophil histamine releasing assay (HR-

urticaria test), samples were sent to the RefLab (Copenhagen, Denmark) and assay was performed using previously published validated reports [22, 23]. Briefly, patient serum in four concentrations (20, 10, 5 and 2.5%) is incubated with IgE-depleted basophil leukocytes (buffycoat). Released histamine is adsorbed onto glass microfibers and detected fluorometrically. Serum-induced histamine release is then expressed as a percentage of total histamine content, and as validation studies showed serum from healthy individuals (n=79) can induce histamine release at maximum 16%, the test is considered positive if the histamine release is >16.5% [22].

The primary end point was adequate control of CU without the need for systemic corticosteroid or immunosuppressive therapy. Patients were seen at various time points and as the validated UAS were not used to document control of disease, the score could not be employed for statistical analyses.

Statistical analyses: Measures of descriptive statistics were used for initial analysis (Microsoft Excel 2007). Nonparametric statistical data were calculated using the GraphPad Prism software Version 5.04 (GraphPad Software,

Inc., La Jolla, CA, USA).

A search of the English-language literature was performed using the following databases (between the years 2009-2011): MEDLINE, BNI, EMBASE, HMIC, CINAHL and Wiley Interscience. The search terms used were 'urticaria AND montelukast', 'urticaria AND leukotriene'. Reports with n<5 patients were excluded from this search.

RESULTS

25 consecutive patients who received montelukast for CIU during the years 2008-2011 were identified from clinic letters. There were 10 males and 15 females with median age at 33 years (age range, 13-66 years). The average duration of urticaria was 3.8 years (duration range, 0.5-12 years). 21 of 25 patients were on both anti-H1 and anti-H2 blockers when montelukast 10mg once daily at night was started. The average duration of use of anti-H1 therapy in all patients was 1.4 years (range, 0.3-8 years) (Table 2). Five patients had evidence of other immunoregulatory disorders (4 with diabetes, 1 hypothyroidism) (Table 2).

Table 2. Clinical Characteristics of Patients with Details of Antihistamines Used for Chronic Urticaria

Age	Gender	Duration of Urticaria (yrs)	Allergies	Co-Existing Immuno-Regulatory Disorders	Antihistamines	Anti-H1 and H2	Duration of Anti-H1 Use (Years)
38	Male	8	Nil	Diabetes	Cetirizine 10 bd	Yes	8
32	Female	4	Nil		Fexofenadine 180 bd and cetirizine 10mg bd	Yes	4
59	Male	4	Yes		Fexofenadine 180 od	Yes	1
33	Female	12	Nil		Cetirizine 10 bd	Yes	0.6
64	Female	9	Aspirin	Diabetes	Fexofenadine 180 bd	Yes	2
28	Male	1	Dust mite/cod		Fexofenadine 180 bd and cetirizine 10mg bd	Yes	1
45	Female	6	Nil		Fexofenadine 180 bd	Yes	1
13	Female	4	Nil		Cetirizine 10 bd	Yes	1
44	Female	2	Dust mite	Diabetes	Fexofenadine 180 od	Yes	0.5
27	Female	0.5	Nil		Fexofenadine 180 bd	Yes	0.5
50	Female	17	Grass pollen		Fexofenadine 180 bd and cetirizine 10mg bd	Yes	0.2
27	Male	4	Nil		Fexofenadine 180 bd	Yes	0.4
17	Male	2	Nil		Cetirizine 10 bd	Yes	1
33	Female	1	Nil		Cetirizine 10 bd	No	1
47	Female	1	Nil		Fexofenadine 180 bd and cetirizine 10mg bd	No	0.5
66	Female	3	Grass pollen	Diabetes	Fexofenadine 180 od	No	2
61	Male	2	Nil		Fexofenadine 180 bd	Yes	0.3
18	Female	2	Nil		Fexofenadine 180 bd and cetirizine 10mg bd	Yes	0.3
42	Male	1	Nil		Fexofenadine 180 od	No	1
23	Male	1	Nil		Cetirizine 10 bd	Yes	0.5
38	Female	1	Dust mite	Hypo-thyroidism	Fexofenadine 180 bd	Yes	0.5
14	Male	1	Nil		Fexofenadine 180 bd	Yes	0.5
51	Female	1	Nil		Fexofenadine 180 bd and cetirizine 10mg bd	Yes	0.5
21	Female	4	Nil		Fexofenadine 180 bd and cetirizine 10mg bd	Yes	3.5
29	Male	4	Nil		Fexofenadine 180 bd and cetirizine 10mg bd	Yes	3.5

12 of 25 patients (8 males, 4 females) or 48% were better after start of montelukast as added therapy along with anti-H1 and anti-H2 blockade for the urticaria. There was no statistical significance between median age between males and females and significant response to montelukast (Mann-Whitney, unpaired t-test (two-tailed) $p=0.57$). There was also no significance between duration of urticaria in males and females and significant response to montelukast (Mann-Whitney, unpaired t-test (two-tailed) with Gaussian approximation, $p=0.42$). 11 patients had no difference to their symptoms of urticaria and in 2 patients the urticaria worsened after montelukast was started. Five patients had side effects (nausea [1], dyspepsia [1], depression [1], and worsening urticaria [2]) that affected the duration of use and may be the outcome (Table 3).

Full blood count revealed basopenia in 15 patients of which 5 responded to montelukast (Table 4). Two patients had positive antinuclear antibody (ANA), 3 with positive thyroid peroxidase antibodies and 4 with positive basophil histamine release (HR-urticaria test) (Table 4). Only one patient had positive ANA,

thyroid peroxidase antibodies and HR-urticaria test who developed depressive symptoms after montelukast was started that necessitated stoppage of therapy. All 20 patients whose complement C3, C4 levels were checked were within normal limits (reference range for our laboratory, C3 0.9-1.8g/L and C4 0.1-0.4g/L). As regards allergies, one patient was sensitive to aspirin/non-steroidal anti-inflammatory drugs who stopped montelukast after one month as there was no benefit. Six patients had positive specific IgE that ranged between Grade 1 to Grade 3 of whom 4 (66%) responded to montelukast along with anti-H1 and anti-H2 therapy.

We found 6 reports on the several databases [53-58] on the efficacy of montelukast in urticaria between the years 2009-2011 (Table 5), since publication of the extensive review by Di Lorenzo *et al.* [59].

CONCLUSIONS

The leukotriene receptor antagonist, montelukast, along with anti-H1/H2 therapy was effective in almost half of our

Table 3. Clinical Characteristics of Patients with Chronic Urticaria and Response to Montelukast

Age	Gender	Duration of Urticaria (yrs)	Anti-H1 and H2	Duration of Anti-H1 Use (Years)	Response to Montelukast	Duration of Use of Montelukast	S/E of LTRA
38	Male	8	Yes	8	No difference	2 weeks	Yes*
32	Female	4	Yes	4	No difference	2 months	no
59	Male	4	Yes	1	Better	3 yrs	Yes**
33	Female	12	Yes	0.6	No difference	1 month	no
64	Female	9	Yes	2	No difference	1 month	no
28	Male	1	Yes	1	Better	5 months and ongoing	no
45	Female	6	Yes	1	Better	5 months and ongoing	no
13	Female	4	Yes	1	Better	4 months	no
44	Female	2	Yes	0.5	Better	6 months	no
27	Female	0.5	Yes	0.5	No difference	3 weeks	no
50	Female	17	Yes	0.2	No difference	8 months	no
27	Male	4	Yes	0.4	Better	3 months and ongoing	no
17	Male	2	Yes	1	Better	5 months and ongoing	no
33	Female	1	No	1	Worse	1 month	Yes ^{ss}
47	Female	1	No	0.5	No difference	6 weeks	no
66	Female	3	No	2	No difference	1 month	no
61	Male	2	Yes	0.3	No difference	2 months	no
18	Female	2	Yes	0.3	No difference	1 week	Yes ^s
42	Male	1	No	1	Better	5 months and ongoing	no
23	Male	1	Yes	0.5	Better	2 months and ongoing	no
38	Female	1	Yes	0.5	Better	2 months and ongoing	no
14	Male	1	Yes	0.5	Better	6 months	no
51	Female	1	Yes	0.5	Worse	2 weeks	Yes ^{ss}
21	Female	4	Yes	3.5	No difference	3 months	no
29	Male	4	Yes	3.5	Better	6 months and ongoing	no

Side effect profile: *nausea, **dyspepsia, ^sdepression, ^{ss}worsening urticaria.

Table 4. Laboratory Results of Patients on Montelukast for Urticaria

Age	Gender	Basopenia on Full Blood Count	ANA	TPOAb	Complement C3, C4	Basophil Histamine Release Test	Positive Specific IgE
38	Male	Yes	Negative		Normal		No
32	Female	Yes	Negative	Negative	Normal		
59	Male	No	Negative*		Normal		Yes (tree pollen, Grade 2)
33	Female	No	Negative	Negative	not done	Negative	No
64	Female	Yes	Negative	Negative	Normal		No [§]
28	Male	No		Negative	not done	Positive 21%	Yes (house dust mite, Grade 3; cod, Grade 2; mixed grasses grade 2)
45	Female	Yes	Positive 1:640	Negative	Normal	Negative	No
13	Female	No		Positive	Normal	Positive 27%	No
44	Female	Yes	Negative	Positive	Normal	Negative	Yes (house dust mite, Grade 1)
27	Female	Yes	Negative	Negative	Normal	Positive 18.5%	
50	Female	Yes		Negative	Normal	Negative	Yes (grass pollen, Grade 3)
27	Male	Yes		Negative	Normal	Negative	No
17	Male	No		Negative	not done		
33	Female	Yes	Negative	Negative	Normal	Negative	No
47	Female	Yes	Negative		Normal		
66	Female	Yes	Negative		Normal		Yes (grass pollen, Grade 2)
61	Male	No			not done		No
18	Female	No	Positive 1:1280	Positive	Normal	Positive 42%**	No
42	Male	No	Negative	Negative	Normal		
23	Male	No	Negative		Normal		No
38	Female	Yes	Negative	Negative	not done	Negative	Yes (house dust mite, Grade 2; mixed grasses Grade 1)
14	Male	No			Normal		No
51	Female	Yes	Negative	Negative	Normal	Negative	No
21	Female	Yes	Negative	Negative	Normal	Negative	No
29	Male	Yes	Negative	Negative	Normal	Negative	No

[§]This patient was allergic to aspirin/non-steroidal anti-inflammatory agents.

*This patient was also positive for M2 mitochondrial antibodies.

**Basophil histamine release test (HR-urticaria test) was negative (<16.5%) on two subsequent occasions, after montelukast was stopped, when urticaria was controlled on fexofenadine 100mg twice daily and doxepin 100mg.

Blank fields suggest tests were not done or results not available.

Specific IgE (kU/L) Allergen Grade interpretation.

0.00 - 0.34 = Grade 0.

0.35 - 0.70 = Grade 1.

0.71 - 3.50 = Grade 2.

3.51 - 17.5 = Grade 3.

17.51 - 50.0 = Grade 4.

50.01 - 100 = Grade 5.

>100 = Grade 6.

patients with CU. The excellent safety profile, non-requirement of regular monitoring with blood tests, wide availability and endorsement by consensus guidelines was the reasons why leukotriene receptor antagonists were considered as the preferred supplementary agents in our cohort of patients. Five patients had side effects (including two patients whose urticaria worsened within 2 weeks) that affected the duration of use and may be the outcome.

We were unable to find any laboratory features that were associated with a response to montelukast. We also recognize the limitation of the automated basophil count that we used for assessment of basophil numbers in the peripheral circulation in patients with urticaria [60], including the possible effect on the basophil numbers with use of certain medications [60-62], although these patients were excluded in our study. The autologous serum skin test is not available at our clinic and therefore the HR-urticaria

Table 5. Reports of Use and Efficacy of Montelukast or Zafirlukast in Chronic Urticaria (Years 2009-2011)

Study Published Year/Country	Number of Patients/Trial Type	Clinical Details and Treatment Groups (if Any)	% Efficacy of the Leukotriene Inhibitor	Reference
2011/Slovenia	22/double-blind crossover study	Chronic idiopathic urticaria	5 of 22 (22.7%)	[53]
2011/Philippines	29/randomized double-blind placebo controlled study	n=14 received montelukast, n=15 placebo for 4 weeks	Decrease in mean UAS in treatment group at 2 weeks	[54]
2011/Japan	76/montelukast trial in 5 patients	NSAID-induced urticaria and angioedema	2 of 5 (40%)	[55]
2010/India	100/montelukast 10mg and levocetirizine 5mg for at least 3 weeks	Chronic urticaria Age range, 4 to 72 years	46% complete improvement	[56]
2009/Taiwan	120/single-blind randomly assigned to 4 groups (107 patients completed)	4 Groups A: anti-H1 only B: anti-H1+anti-H2 C: anti-H1+LTRA D: placebo	53% (Group C)	[57]
2009/Finland	45/randomized double-blind placebo-controlled crossover	Pollen-sensitized patients (atopic) with urticaria; done during the 2007 pollen season	No difference between montelukast and placebo	[58]

test was used to determine the severity of urticaria in our patients, but the test was unhelpful in being able to determine whether leukotriene inhibition was more likely to have an effect.

Although some studies may suggest that use of leukotriene inhibitors may allow a persistent drug-free remission, most reports argue against such a disease-modifying effect. We were unable to verify this as patients continue to remain on montelukast once it has proven effective in controlling the disease activity. More head-to-head clinical trials are required, including using drugs such as dapson [63], to see which subgroups of patients' are more likely to respond to which types of medications until reliable laboratory markers becomes available. Finally, the potential of naturally occurring products with anti-inflammatory and anti-allergic roles should not be ignored as these may well be treatments of the future [64-66].

ACKNOWLEDGEMENT

Declared none.

CONFLICT OF INTEREST

Declared none.

REFERENCES

- Zuberbier, T.; Asero, R.; Bindslev-Jensen, C.; Canonica, W.G.; Church, M.K.; Giménez-Arnau, A.M.; Grattan, C.E.; Kapp, A.; Maurer, M.; Merk, H.F.; Rogala, B.; Saini, S.; Sánchez-Borges, M.; Schmid-Grendelmeier, P.; Schünemann, H.; Staubach, P.; Vena, G.A.; Wedi, B.; Dermatology Section of the European Academy of Allergology and Clinical Immunology; Global Allergy and Asthma European Network; European Dermatology Forum; World Allergy Organization. EAACI/GA(2)LEN/EDF/WAO guideline: definition, classification and diagnosis of urticaria. *Allergy*, **2009**, *64*, 1417-1426.
- Zuberbier, T.; Asero, R.; Bindslev-Jensen, C.; Walter Canonica, G.; Church, M.K.; Giménez-Arnau, A.; Grattan, C.E.; Kapp, A.; Merk, H.F.; Rogala, B.; Saini, S.; Sánchez-Borges, M.; Schmid-Grendelmeier, P.; Schünemann, H.; Staubach, P.; Vena, G.A.; Wedi, B.; Maurer, M.; Dermatology Section of the European Academy of Allergology and Clinical Immunology; Global Allergy and Asthma European Network; European Dermatology Forum; World Allergy Organization. EAACI/GA(2)LEN/EDF/WAO guideline: definition, classification and diagnosis of urticaria. *Allergy*, **2009**, *64*, 1417-1426.
- Maurer, M.; Weller, K.; Bindslev-Jensen, C.; Giménez-Arnau, A.; Bousquet, P.J.; Bousquet, J.; Canonica, G.W.; Church, M.K.; Godse, K.V.; Grattan, C.E.; Greaves, M.W.; Hide, M.; Kalogeromitros, D.; Kaplan, A.P.; Saini, S.S.; Zhu, X.J.; Zuberbier, T. Unmet clinical needs in chronic spontaneous urticaria. A GA²LEN task force report. *Allergy*, **2011**, *66*, 317-330.
- Kaplan, A. Chronic urticaria and angioedema. *N. Eng. J. Med.*, **2002**, *346*, 175-179.
- Lipworth, B.J. Leukotriene-receptor antagonists. *Lancet*, **1999**, *353*, 57-62.
- Brunetti, L.; Francavilla, R.; Miniello, V.L.; Platzer, M.H.; Rizzi, D.; Lospalluti, M.L.; Poulsen, L.K.; Armenio, L.; Skov, P.S. High prevalence of autoimmune urticaria in children with chronic urticaria. *J. Allergy Clin. Immunol.*, **2004**, *114*, 922-927.
- Takeda, T.; Sakurai, Y.; Takahagi, S.; Kato, J.; Yoshida, K.; Yoshioka, A.; Hide, M.; Shima, M. Increase of coagulation potential in chronic spontaneous urticaria. *Allergy*, **2011**, *66*, 428-433.
- Huilan, Z.; Runxiang, L.; Bihua, L.; Qing, G. Role of the subgroups of T, B, natural killer lymphocyte and serum levels of interleukin-15, interleukin-21 and immunoglobulin E in the pathogenesis of urticaria. *J. Dermatol.*, **2010**, *37*, 441-447.
- Raap, U.; Wiczorek, D.; Gehring, M.; Pauls, I.; Ständer, S.; Kapp, A.; Wedi, B. Increased levels of serum IL-31 in chronic spontaneous urticaria. *Exp. Dermatol.*, **2010**, *19*, 464-466.
- Kasperska-Zajac, A.; Brzoza, Z.; Rogala, B. Increased concentration of platelet-derived chemokines in serum of patients with delayed pressure urticaria. *Eur. Cytokine Netw.*, **2008**, *19*, 89-91.
- Dos Santos, J.C.; Azor, M.H.; Nojima, V.Y.; Lourenço, F.D.; Prearo, E.; Maruta, C.W.; Rivitti, E.A.; da Silva Duarte, A.J.; Sato, M.N. Increased circulating pro-inflammatory cytokines and imbalanced regulatory T-cell cytokines production in chronic idiopathic urticaria. *Int. Immunopharmacol.*, **2008**, *8*, 1433-1440.
- Chen, W.C.; Chiang, B.L.; Liu, H.E.; Leu, S.J.; Lee, Y.L. Defective functions of circulating CD4⁺CD25⁺ and CD4⁺CD25⁻ T cells in patients with chronic ordinary urticaria. *J. Dermatol. Sci.*, **2008**, *51*, 121-130.
- Lourenço, F.D.; Azor, M.H.; Santos, J.C.; Prearo, E.; Maruta, C.W.; Rivitti, E.A.; Duarte, A.J.; Sato, M.N. Activated status of basophils in chronic urticaria leads to interleukin-3 hyper-responsiveness and enhancement of histamine release induced by anti-IgE stimulus. *Br. J. Dermatol.*, **2008**, *158*, 979-986.
- Caproni, M.; Giomi, B.; Melani, L.; Volpi, W.; Antiga, E.; Torchia, D.; Fabbri, P. Cellular infiltrate and related cytokines, chemokines, chemokine receptors and adhesion molecules in chronic autoimmune urticaria: comparison between spontaneous and

- autologous serum skin test induced wheal. *Int. J. Immunopathol. Pharmacol.*, **2006**, *19*, 507-515.
- [15] Puccetti, A.; Bason, C.; Simeoni, S.; Millo, E.; Tinazzi, E.; Beri, R.; Peterlana, D.; Zanoni, G.; Senna, G.; Corrocher, R.; Lunardi, C. In chronic idiopathic urticaria autoantibodies against Fc epsilonR2/CD23 induce histamine release via eosinophil activation. *Clin. Exp. Allergy*, **2005**, *35*, 1599-1607.
 - [16] Kasperska-Zajac, A.; Rogala, B.; Nowakowski, M. Assessment of platelet activity as expressed by plasma levels of platelet factor 4 and beta-thromboglobulin in patients with chronic idiopathic urticaria. *Exp. Dermatol.*, **2005**, *14*, 515-518.
 - [17] Caproni, M.; Giomi, B.; Volpi, W.; Melani, L.; Schincaglia, E.; Macchia, D.; Manfredi, M.; D'Agata, A.; Fabbri, P. Chronic idiopathic urticaria: infiltrating cells and related cytokines in autologous serum-induced wheals. *Clin. Immunol.*, **2005**, *114*, 284-292.
 - [18] Caproni, M.; Cardinali, C.; Giomi, B.; Antiga, E.; D'Agata, A.; Walter, S.; Fabbri, P. Serological detection of eotaxin, IL-4, IL-13, IFN-gamma, MIP-1alpha, TARC and IP-10 in chronic autoimmune urticaria and chronic idiopathic urticaria. *J. Dermatol. Sci.*, **2004**, *36*, 57-59.
 - [19] Santos, J.C.; de Brito, C.A.; Futata, E.A.; Azor, M.H.; Oriei, N.M.; Maruta, C.W.; Rivitti, E.A.; Duarte, A.J.; Sato, M.N. Up-regulation of chemokine C-C ligand 2 (CCL2) and C-X-C chemokine 8 (CXCL8) expression by monocytes in chronic idiopathic urticaria. *Clin. Exp. Immunol.*, **2012**, *167*, 129-136.
 - [20] Tedesco, F.; Pucillo, C. Mast cells are critically involved in serum-mediated vascular leakage in chronic urticaria beyond high-affinity IgE receptor stimulation. *Allergy*, **2011**, *66*, 1538-1545.
 - [21] Ferrer, M.; Nuñez-Córdoba, J.M.; Luquin, E.; Grattan, C.E.; De la Borbolla, J.M.; Sanz, M.L.; Schwartz, L.B. Serum total tryptase levels are increased in patients with active chronic urticaria. *Clin. Exp. Allergy*, **2010**, *40*, 1760-1766.
 - [22] Platzer, M.H.; Grattan, C.E.; Poulsen, L.K.; Skov, P.S. Validation of basophil histamine release against the autologous serum skin test and outcome of serum-induced basophil histamine release studies in a large population of chronic urticaria patients. *Allergy*, **2005**, *60*, 1152-1156.
 - [23] Asero, R.; Lorini, M.; Chong, S.U.; Zuberbier, T.; Tedeschi, A. Assessment of histamine-releasing activity of sera from patients with chronic urticaria showing positive autologous skin test on human basophils and mast cells. *Clin. Exp. Allergy*, **2004**, *34*, 1111-1114.
 - [24] Di Leo, E.; Nettis, E.; Aloia, A.M.; Moschetta, M.; Carbonara, M.; Dammacco, F.; Vacca, A. Cyclosporin-A efficacy in chronic idiopathic urticaria. *Int. J. Immunopathol. Pharmacol.*, **2011**, *24*, 195-200.
 - [25] Boubouka, C.D.; Charissi, C.; Kouimintzis, D.; Kalogeromitros, D.; Stavropoulos, P.G.; Katsarou, A. Treatment of autoimmune urticaria with low-dose cyclosporin A: A one-year follow-up. *Acta Derm. Venereol.*, **2011**, *91*, 50-54.
 - [26] Kessel, A.; Toubi, E. Cyclosporine-A in severe chronic urticaria: the option for long-term therapy. *Allergy*, **2010**, *65*, 1478-1482.
 - [27] Ohtsuka, T. Response to oral cyclosporine therapy and high sensitivity-CRP level in chronic idiopathic urticaria. *Int. J. Dermatol.*, **2010**, *49*, 579-584.
 - [28] Serhat Inaloz, H.; Ozturk, S.; Akcali, C.; Kirtak, N.; Tarakcioglu, M. Low-dose and short-term cyclosporine treatment in patients with chronic idiopathic urticaria: a clinical and immunological evaluation. *J. Dermatol.*, **2008**, *35*, 276-282.
 - [29] Godse, K.V. Cyclosporine in chronic idiopathic urticaria with positive autologous serum skin test. *Indian J. Dermatol.*, **2008**, *53*, 101-102.
 - [30] Vena, G.A.; Cassano, N.; Colombo, D.; Peruzzi, E.; Pigatto, P. Neo-I-30 Study Group. Cyclosporine in chronic idiopathic urticaria: a double-blind, randomized, placebo-controlled trial. *J. Am. Acad. Dermatol.*, **2006**, *55*, 705-709.
 - [31] Baskan, E.B.; Tunalı, S.; Turker, T.; Saricaoglu, H. Comparison of short- and long-term cyclosporine A therapy in chronic idiopathic urticaria. *J. Dermatolog. Treat.*, **2004**, *15*, 164-168.
 - [32] Loria, M.P.; Dambra, P.P.; D'Oronzio, L.; Nettis, E.; Pannofino, A.; Cavallo, E.; Ferrannini, A.; Tursi, A. Cyclosporin A in patients affected by chronic idiopathic urticaria: a therapeutic alternative. *Immunopharmacol. Immunotoxicol.*, **2001**, *23*, 205-213.
 - [33] Darras, S.; Ségard, M.; Mortier, L.; Bonneville, A.; Thomas, P. Treatment of solar urticaria by intravenous immunoglobulins and PUVA therapy. *Ann. Dermatol. Venereol.*, **2004**, *131*, 65-69.
 - [34] Aydoğan, K.; Karadogan, S.K.; Tunalı, S.; Saricaoglu, H. Narrowband ultraviolet B (311nm, TL01) phototherapy in chronic ordinary urticaria. *Int. J. Dermatol.*, **2012**, *51*, 98-103.
 - [35] Engin, B.; Ozdemir, M.; Balevi, A.; Mevlitoğlu, I. Treatment of chronic urticaria with narrowband ultraviolet B phototherapy: a randomized controlled trial. *Acta Derm. Venereol.*, **2008**, *88*, 247-251.
 - [36] Monfrecola, G.; de Paulis, A.; Prizio, E.; Russo, I.; Carfora, M.; Santoianni, P.; Marone, G. *In vitro* effects of ultraviolet A on histamine release from human basophils. *J. Eur. Acad. Dermatol. Venereol.*, **2003**, *17*, 646-651.
 - [37] Berroeta, L.; Clark, C.; Ibbotson, S.H.; Ferguson, J.; Dawe, R.S. Narrow-band (TL-01) ultraviolet B phototherapy for chronic urticaria. *Clin. Exp. Dermatol.*, **2004**, *29*, 97-98.
 - [38] Nettis, E.; D'Erasmo, M.; Di Leo, E.; Calogiuri, G.; Montinaro, V.; Ferrannini, A.; Vacca, A. The employment of leukotriene antagonists in cutaneous diseases belonging to allergological field. *Mediators Inflamm.*, **2010**, *2010*.
 - [39] Scadding, G.W.; Scadding, G.K. Recent advances in antileukotriene therapy. *Curr. Opin. Allergy Clin. Immunol.*, **2010**, *10*, 370-376.
 - [40] Rovati, G.E.; Capra, V. Cysteinyl-leukotriene receptors and cellular signals. *Sci. World J.*, **2007**, *7*, 1375-1392.
 - [41] Riccioni, G.; Bucciarelli, T.; Mancini, B.; Di Ilio, C.; D'Orazio, N. Antileukotriene drugs: clinical application, effectiveness and safety. *Curr. Med. Chem.*, **2007**, *14*, 1966-1977.
 - [42] Leonardi, S.; Marchese, G.; Marseglia, G.L.; La Rosa, M. Montelukast in allergic diseases beyond asthma. *Allergy Asthma Proc.*, **2007**, *28*, 287-291.
 - [43] McBayne, T.O.; Siddall, O.M. Montelukast treatment of urticaria. *Ann. Pharmacother.*, **2006**, *40*, 939-942.
 - [44] Asero, R.; Tedeschi, A.; Lorini, M. Leukotriene receptor antagonists in chronic urticaria. *Allergy*, **2001**, *56*, 456-457.
 - [45] Di Lorenzo, G.; Pacor, M.L.; Mansueto, P.; Esposito Pelleriti, M.; Lo Bianco, C.; Ditta, V.; Martinelli, N.; Rini, G.B. Randomized placebo-controlled trial comparing desloratadine and montelukast in monotherapy and desloratadine plus montelukast in combined therapy for chronic idiopathic urticaria. *J. Allergy Clin. Immunol.*, **2004**, *114*, 619-625.
 - [46] Nettis, E.; Colanardi, M.C.; Paradiso, M.T.; Ferrannini, A. Desloratadine in combination with montelukast in the treatment of chronic urticaria: a randomized, double-blind, placebo-controlled study. *Clin. Exp. Allergy*, **2004**, *34*, 1401-1407.
 - [47] Nettis, E.; Colanardi, M.C.; Soccio, A.L.; Ferrannini, A.; Vacca, A. Desloratadine in combination with montelukast suppresses the dermatographometer challenge test papule, and is effective in the treatment of delayed pressure urticaria: a randomized, double-blind, placebo-controlled study. *Br. J. Dermatol.*, **2006**, *155*, 1279-1282.
 - [48] Godse, K.V. Oral montelukast monotherapy is ineffective in chronic idiopathic urticaria: a comparison with oral cetirizine. *Indian J. Dermatol. Venereol. Leprol.*, **2006**, *72*, 312-314.
 - [49] Sanada, S.; Tanaka, T.; Kameyoshi, Y.; Hide, M. The effectiveness of montelukast for the treatment of anti-histamine-resistant chronic urticaria. *Arch. Dermatol. Res.*, **2005**, *297*, 134-138.
 - [50] Erbagci, Z. The leukotriene receptor antagonist montelukast in the treatment of chronic idiopathic urticaria: a single-blind, placebo-controlled, crossover clinical study. *J. Allergy Clin. Immunol.*, **2002**, *110*, 484-488.
 - [51] Mathias, S.D.; Crosby, R.D.; Zazzali, J.L.; Maurer, M.; Saini, S.S. Evaluating the minimally important difference of the urticaria activity score and other measures of disease activity in patients with chronic idiopathic urticaria. *Ann. Allergy Asthma Immunol.*, **2012**, *108*, 20-24.
 - [52] Mathias, S.D.; Dreskin, S.C.; Kaplan, A.; Saini, S.S.; Spector, S.; Rosén, K.E. Development of a daily diary for patients with chronic idiopathic urticaria. *Ann. Allergy Asthma Immunol.*, **2010**, *105*, 142-148.
 - [53] Kosnik, M.; Subic, T. Add-on montelukast in antihistamine-resistant chronic idiopathic urticaria. *Respir. Med.*, **2011**, *105*, S84-8.
 - [54] Agcaoili, M.L.; Sumpaico, M.W.; Aleta, L.A.; Recto, M.P.; Abong, J.M. Montelukast in the treatment of chronic Urticaria: A

- randomized double blind, placebocontrolled study. *Ann. Allergy Asthma Immunol.*, **2011**, 107/5 SUPPL. 1(A17), 1081-1206.
- [55] Moriya, M.; Aihara, M.; Hirota, R.; Hirata, Y.; Ikinaga, N.; Takamura, N.; Kunimi, Y.; Uchida, T.; Ikezawa, Z. Analysis of 76 patients with urticaria and angioedema induced by non-steroidal anti-inflammatory drugs (NSAIDs) in Japan. *Arerugi*, **2011**, 60, 699-707.
- [56] Kumar, S. Effect of montelukast and levocetirizine for antihistamine resistance chronic urticaria. *Allergy*, **2010**, 65, 457-458.
- [57] Wan, K.S. Efficacy of leukotriene receptor antagonist with an anti-H1 receptor antagonist for treatment of chronic idiopathic urticaria. *J. Dermatolog. Treat.*, **2009**, 20, 194-197.
- [58] Lehtimäki, L.; Petäys, T.; Haahtela, T. Montelukast is not effective in controlling allergic symptoms outside the airways: a randomised double-blind placebo-controlled crossover study. *Int. Arch Allergy Immunol.*, **2009**, 149, 150-153.
- [59] Di Lorenzo, G.; D'Alcamo, A.; Rizzo, M.; Leto-Barone, M.S.; Bianco, C.L.; Ditta, V.; Politi, D.; Castello, F.; Pepe, I.; Di Fede, G.; Rini, G. Leukotriene receptor antagonists in monotherapy or in combination with antihistamines in the treatment of chronic urticaria: a systematic review. *J. Asthma Allergy*, **2008**, 9, 9-16.
- [60] Grattan, C.E.H.; Dawn, G.; Gibbs, S.; Francis, D.M. Blood basophil numbers in chronic ordinary urticaria and healthy controls: diurnal variation, influence of loratadine and prednisolone and relationship to disease activity. *Clin. Exp. Allergy*, **2003**, 33, 337-341.
- [61] Leonard, E.J. Two populations of human blood basophils: effect of prednisone on circulating numbers. *J. Allergy Clin. Immunol.*, **1987**, 79, 775-780.
- [62] Kawakami, A.; Suzukawa, M.; Koketsu, R.; Komiya, A.; Ohta, K.; Yamamoto, K.; Yamaguchi, M. Enhancement of basophil apoptosis by olopatadine and theophylline. *Allergy Asthma Proc.*, **2008**, 29, 322-8.
- [63] Grundmann, S.A.; Kiefer, S.; Luger, T.A.; Brehler, R. Delayed pressure urticaria - dapsone heading for first-line therapy? *J. Dtsch. Dermatol. Ges.*, **2011**, 9, 908-9012.
- [64] Vo, T.S.; Ngo, D.H.; Kim, S.K. Potential Targets for Anti-Inflammatory and Anti-Allergic Activities of Marine Algae: An Overview. *Inflamm. Allergy Drug Targets*, **2012**, 11, 90-101.
- [65] Nualsanit, T.; Rojanapanthu, P.; Gritsanapan, W.; Kwankitpraniti, T.; Min, K.W.; Baek, S.J. Damnacanthol-induced anti-inflammation is associated with inhibition of NF- κ B activity. *Inflamm. Allergy Drug Targets*, **2011**, 10, 455-463.
- [66] Broderick, L.; Tourangeau, L.M.; Kavanaugh, A.; Wasserman, S.I. Biologic modulators in allergic and autoimmune diseases. *Curr. Opin. Allergy Clin. Immunol.*, **2011**, 11, 355-360.

Received: January 17, 2012

Revised: March 4, 2012

Accepted: March 6, 2012