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Research Article

Effects of H1 antihistamine therapy on the cytokine profile in chronic urticaria

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Abstract. Aim: to assess the variation in pro and anti-inflammatory cytokines: IL-1β, IL-2, IL-4, IL-6, IL-10, IFN γ, TNF-α, IL-17 and IL-31 under treatment with second-generation H1 antihistamines, Levocetirizine and Desloratadine. Materials and methods: patients diagnosed with chronic urticaria without background therapy with H1 antihistamines or cortisone in the past three months were included in the study. Patient evaluation included medical history and a specific questionnaire for assessing disease severity. They were regularly followed up for up to 3 months in order to adjust the treatment. Blood samples, required for cytokine assay (IL-1β, IL-2, IL-4, IL-6, IL-10, IFN-γ, TNF-α, IL-17 and IL-31) were collected at baseline and 3 months after initiation of treatment. Results: Disease control was achieved in all patients 3 months after initiation of therapy, but patients had different treatment regimens. A percentage of 71.1% of patients responded favorably to treatment with second-generation H1 antihistamines (Desloratadine and Levocetirizine), but at various doses. Pro-inflammatory cytokines decreased significantly under treatment, while IL-10, an anti-inflammatory cytokine, had no significant variations. When comparing the two studied antihistamines, Desloratadine and Levocetirizine, there was no significant difference between the two in terms of reduced cytokine levels, except for IL-1, which decreased significantly more in the group of patients treated with Desloratadine. Conclusions: in most cases, H1 antihistamines provided chronic urticaria symptom control. H1 antihistamines significantly reduce plasma levels of IL-1β, IL-2, IL-4 IL-6, IFN-γ, TNF-α, IL IL-17 and IL-31, but not IL-10 levels. Patients treated with Desloratadine had a greater decrease in IL-1β than those treated with Levocetirizine.

Key Words: chronic urticaria, cytokines, treatment

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Introduction

Chronic urticaria (CU) is defined by the presence of recurrent urticarial lesions, transient, pruritic and erythematous, for a period of at least 6 weeks. The diagnosis of urticaria integrates a heterogeneous group of diseases emerging as a result of a great variety of causes (Zuberbier et al 2009). All types and subtypes share a distinctive pattern of skin reactions manifested by urticarial lesions and angioedema.

Urticaria is one of the most common 20 skin diseases, known since antiquity. It is estimated that about 3% of the population of Western Europe suffer from chronic urticarial (Kapplan et al 2009). Even though CU is an easily recognizable disease, which is generally not life threatening, except for rare cases when it is accompanied by severe symptoms of angioedema, it severely affects patients' lives at a level comparable to that of patients suffering from coronary artery disease awaiting surgery for triple bypass (O'Donnell et al 1997).

A significant percentage of all cases of chronic urticaria is represented by chronic autoimmune urticaria, whose name is given by the pathogenic mechanism of production, being mediated by specific anti-FcεRI and/or anti-IgE autoantibodies (Konstantinou et al 2013). In a previous study, we showed that immuno-inflammatory changes occurring in chronic urticaria are a combination of mixed Th1/Th2 as well as Th17 lymphocyte response (Crisan et al 2014). Even if we could not confirm a unique pathogenic mechanism common to all forms of urticaria, it is considered that the mastocyte is the central cell in the pathogenesis of this disease. Mast cells are involved in the early stages of inflammation, generating and releasing a series of cytokines involved in the generation and maintenance of an immune response, such as IL-1β, IL-6, TNF-α or IFN-γ.

IL-1β is an interleukin which plays a key role in the immune response, stimulating the proliferation and differentiation of T lymphocytes. Anti-interleukin-1 therapy (Anakinra or ILIRa) has proven to be effective in auto-inflammatory syndromes including chronic urticaria as a manifestation (Kapplan 2012). IL-2, with a similar function as IL-1β, may also have an anti-inflammatory function, however, by its ability to induce the proliferation of regulatory LyT.

TNF-α secreted mainly by activated macrophages, triggers acute phase response, together with IL-1β. In chronic autoimmune urticaria anti-TNF alpha therapy was effective in 60% of patients who had not previously responded to anti-H1 therapy (Sand 2013). IL-6, dominant pro-inflammatory cytokine, is the most important stimulant of the synthesis of acute phase proteins (APP). However, after its pro-inflammatory action, IL-6 interrupts the inflammatory cascade by inhibiting the synthesis of IL-1β and TNF-α, along with the stimulation of IL-1 receptor antagonist (IL-1Ra) and IL-10. IFN-γ is a type II interferon, with antiviral and immunomodulatory, antibacterial, antitumor function. IFN-γ has the effect of stimulating monocytes/macrophages

and increasing the production of pro-inflammatory cytokines (IL-1β, IL-6 and TNF-α) (Ferrer 2012; Papadopoulos 2014).
IL-17 is a pro-inflammatory cytokine secreted by Th17 Ly, a subset of T helper cells. IL-17 has a pro-inflammatory function, being involved in delayed reactions. It acts synergistically with IL-1 and TNF-α.
The Th2 response is governed by IL-4 synthesis. IL-4 is a cytokine with a defining role of inducing the differentiation of naive Th Ly into Th2 Ly, most probably under the influence of basophils, as shown in recent studies (Sokol et all 2008 and Garcia et all 2011). Overproduction of IL-4 is associated with allergic diseases (Kay et al 1997).
IL-31, a recently discovered cytokine, is secreted by activated T cells and, in particular, by Th2 Ly. Memory T cells, capable of producing IL-31, are present in the skin, where they can contribute to inflammation. In a study conducted on patients with chronic urticaria, serum levels of IL-31 were found to be increased compared to healthy non-atopic controls, but still without a correlation with disease severity (Raap et al 2010).
Interleukin-10, also known as cytokine synthesis inhibitory factor (CSIF), is an anti-inflammatory cytokine expressed in a wide range of cells of the innate and the adaptive immune system. It plays an essential role in regulating the immune response and thus, in the one encountered in chronic urticaria.
Second-generation H1 antihistamines are currently the first-line therapy in chronic spontaneous urticarial (Makris et al 2013; Garcia et al 2013). The main goal of the symptomatic treatment is the reduction of mast cell derived mediators and the prevention of their effects (Zuberbier et al 2009). H1 antihistamines trigger a symptomatic effect, but second-generation antihistamines have proven their anti-inflammatory effects by reducing serum cytokine levels in both chronic urticaria and other allergic conditions (Schroeder 2001; Caproni et al 2006; Ortonne 2012). The doses used in chronic urticaria may be greater than the usual ones, even four times higher (Zuberbier et al 2009).
This study aimed to assess the variation in pro and anti-inflammatory cytokines: IL-1β, IL-2, IL-4, IL-6, IL-10, IFN γ, TNF-α, IL-17 and IL-31 under treatment with second-generation H1 antihistamines, Levocetirizine and Desloratadine.

Materials and methods

Patients

The study included 59 patients with chronic spontaneous urticaria, who presented themselves to the ambulatory care unit of the Municipal Clinical Hospital, Cluj-Napoca, from October 2007 to November 2012. Patients aged over 18 who had daily manifestations of urticaria, with or without angioedema, for at least 6 weeks were included in the study.
The exclusion criteria were as follows: treatment with antihistamines or corticosteroids followed in the last 3 months prior to presentation, presence of malignancy, presence of other severe chronic diseases. Inclusion in the study was done after signing their informed consent form. The study protocol was approved by the Ethics Committee of "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca.

Clinical evaluation

Patients were evaluated by anamnesis and clinical examination in order to highlight the presence and severity of chronic urticaria. Demographic data recorded were: age, gender, duration of disease.
Medical history determined disease activity using the urticaria activity score (UAS). This scale assesses the main clinical features of chronic urticaria: itch intensity and the number of urticarial lesions within 24 hours. The score ranges from 0 to 6 (Zuberbier 2009). For more precise data, it is recommended to perform the UAS analysis for the past 7 days prior to the visit (Zuberbier 2009). UAS 7 was completed at baseline and during each patient visit.
Patients included in the study were evaluated regularly every two weeks in order to adjust the therapy to achieve disease control, for a period of three months.

Treatment

All patients received baseline second-generation H1 antihistamines (Desloratadine or Levocetirizine) 5-10 mg/day, depending on the severity of the disease. Antibiotherapy was associated in case of the presence of bacterial infections. Every 2 weeks, the dose were adjusted upwards or downwards depending on the development, with the possibility of increasing the dose up to 20 mg/day. On subsequent visits, when necessary and when symptoms were not controlled by the quadruple dose, one or more of the following drugs were associated: Montelukast 10 mg, Ranitidine 2x150 mg Doxepin 25 mg. If they also fail to control these symptoms, we recommend the immunosuppressive treatment with Cyclosporine.

Plasma cytokine levels

Serum levels of IL-1β, IL-2, IL-4 IL-6, IL-10, IFN-γ, TNF-α, IL-17 and IL-31 were determined. Blood samples were drawn at baseline and after 3 months of treatment. Blood was centrifuged within one hour after being harvested, followed by separation of the serum and storage at -80^{0}C until determination.
IL-4, IFN-γ, TNF-α, IL-17 and IL-31 were determined using ELISA (Enzyme Linked Immunosorbent Assay), and IL-1β, IL-2, IL-6, IL-10 were determined by means of multiplex plates, using Luminex Performance Human Cytokine Panel A (R&D Systems, Wiesbaden, Germany). Samples and standard dilutions were achieved in accordance with the manufacturer's instructions.

Statistical analysis

SPSS 21 software program was used for statistical analysis. Quantitative data were tested for normality of the distribution by Kolmogorov-Smirnov test. The differences of a quantitative variable between two groups were evaluated using the t test for independent variables or the Mann-Whitney test. Differences in the percentage of a nominal variable between two groups were tested using the Chi-square test or Fisher's exact test. The correlation between two quantitative variables was tested using Spearman's rank correlation coefficient. Continuous variables with normal distribution were characterized by the mean ± SD, while those with non-normal distribution were described by the median (25% percentile, 75% percentile). A p value of <0.05 was considered as the threshold of statistical significance.

Results

The average age of the patients included in the study was 42.6 ± 11.2 years, with a minimum of 18 years and a maximum of

72 years. The age variable had the normal distribution (p>0.05). Nine patients (15.2%) were males, and 50 (84.7%) were females. In terms of area of origin, 16 patients (27.13%) were from rural areas and most of the patients, 43 (72.87%) subjects, were from urban areas.

Symptom control was achieved in all patients in the study on the 3-month visit. Three months after being included in the study, 3 patients (5.1%) did not require background therapy anymore. They have all completed antibiotic treatment, 2 of them being treated for eradication of HP infection. A percentage of 71.1% of patients responded favorably to treatment with second-generation anti-H1.

During the 3-month evaluation, eleven patients (18.6%) had combined treatment with antihistamines and one or more of the following drugs: Ranitidine, Montelukast, Doxepin. Three patients had anti-H1 and cyclosporine as background therapy (5.1%) (Table 1).

Table 1. Patient medication after the 3-month follow-up. The values are expressed in % and number of patients

Medication	Total no.	Women	Men
No medication	3 (5.1%)	2 (66.6%)	1 (33.3%)
Only anti H1	42 (71.1%)	37 (88.1%)	5 (11.9)
Anti-H1+Montelukast	4 (6.8%)	2 (50%)	2 (50%)
Anti-H1+Montelukast+Ranitidine	3 (5.1)	2 (66.6%)	1 (33.3%)
Anti-H1+Montelukast+Ranitidine+Doxepin	4 (6.8%)	4 (100%)	0 (0%)
Anti-H1+Ciclosporine	3 (5.1%)	3 (100%)	0 (0%)

Patients controlled with H1 antihistamines alone received Desloratadine or Levocetirizine, with varying symptom controlling doses (Table 2).

Table 2. Anti-H1 doses that were able to control the symptoms

Anti H1	5 mg/day	10 mg/day	20 mg/day
Desloratadine	7	13	3
Levocetirizine	9	13	-

In the 42 patients treated with H1 antihistamines the cytokine profile was assessed after 3 months of treatment. Table 3 shows that the treatment caused significant decreases in all cytokines. IL-10 was the only cytokine without variations during therapy. Interleukins had non-normally distributed values (p<0.05).

There were no significant differences between the two antihistamines studied, Desloratadine and Levocetirizine, in terms of the decrease in cytokine values. Only IL-1β values recorded significantly greater decreases in patients who were treated with Desloratadine, compared to those who were treated with Levocetirizine (p=0.05; Figure 1).

The reduced values of the cytokines investigated under treatment with H1 antihistamines are not influenced by patient age and gender, area of origin or duration of disease.

Table 3. Cytokine values before and after treatment.

Cytokine	Baseline values	Values after treatment	p
IL-1β	2.49 (2.23; 2.73)	2.43 (2.23; 2.56)	0.002
IL-2	0.21 (0.05; 0.61)	0. 21 (0.19; 0.55)	0.003
IL-4	3 (0; 30)	2 (0; 18)	0.01
IL-6	2.43 (1.29; 3.63)	1.71. (1.03; 2.32)	0.002
IL-10	0.62 (0.23; 1.06)	(0.63 (0.23; 1.05)	0.1
TNF-α	3.8 (0; 93)	3 (0; 80)	0.02
IFN-γ	10 (8; 14)	8 (6; 12)	0.01
IL-17	9.1 (0; 30)	6.1 (0; 28)	0.01
IL-31	808 (0; 12815)	488 (0; 4400)	0.01

Values are expressed as median and 25-75th percentiles. A p value <0.05 was considered statistically significant.

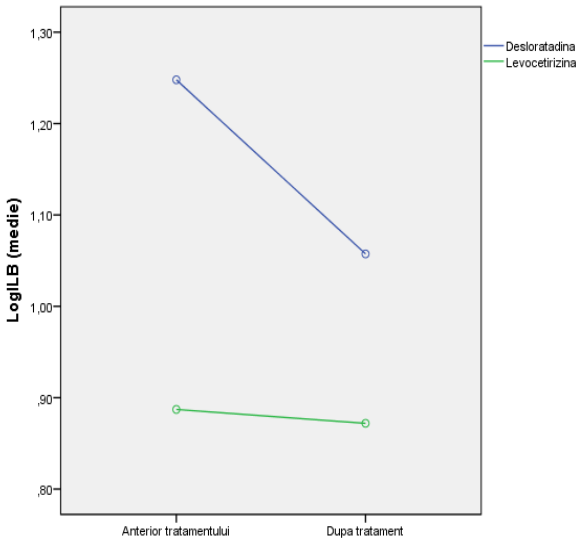

Figure 1. IL-1β evolution under treatment with Desloratadine and Levocetirizine

Discussion

The study assesses the anti-inflammatory effect of certain second-generation antihistamines in patients with chronic spontaneous urticaria. The study shows that second-generation antihistamines, Desloratadine and Levocetirizine, can control the symptoms of chronic urticaria, in standard dose or higher doses, as well as the pro-inflammatory parameters involved in the pathogenesis of chronic urticaria.

Treatment of chronic urticaria is generally a dynamic one. Initially directed against possible influencial etiological factors, in most cases it becomes symptomatic, lengthy, requiring periodic changes in order to achieve the minimum treatment that can control the disease. This study also observed that most patients were controlled by means of monotherapy (H1 antihistamines), but 23.4% of patients required combination therapy in order to control disease symptoms.

The study shows good control of disease activity with H1 antihistamines, data being similar to other studies in the literature.

Staevska et al (2010) have shown that 75% of patients with chronic urticaria were controlled with H1 antihistamines, Levocetirizine or Desloratadine after 1 month of treatment. But only 16.5% of patients could be controlled with standard doses of antihistamines (5 mg/day), compared to the present study where 38% of patients treated with H1 antihistamines could be controlled using the standard dose. However, in the present study doses were increased every two weeks, not weekly as in the study conducted by Staevska, and the final evaluation was performed after 3 months of treatment, not after 4 weeks. Those differences can be explained by the heterogeneity of chronic urticaria, and the longer duration of the treatment. It is possible that a long-term treatment would be able to control the disease and progressively reduce the doses to the standard dose. It is well known that the placebo effect is very high in patients with chronic urticaria, so the results obtained in open trials must be carefully interpreted.

Leukotrienes are mediators involved in the pathogenesis of CU. The association with Montelukast (10 mg /day), a leukotriene receptor antagonist (LTRA), may provide an optimal management of disease symptoms. In the present study, the association of Montelukast (10 mg/day) improved symptom control, but only in a small percentage of patients (6.7%), which had also been mentioned in other studies (Nettis et al 2004; Kosnik 2011). However, 16.7% of patients require the association with H2 antihistamines, doxepin or immunosuppressants.

Another question that arises is related to the choice of the right antihistamine for the treatment of CU. In our study, both antihistamines were able to control CU symptoms after 3 months of treatment. However, 3 patients required 2010,maximal doses of Desloratadine, 20 mg/day. Data are similar to those obtained by Staevska showing that Levocetirizine provides a better control of disease activity compared to Desloratadine after 4 weeks of treatment.

It is widely accepted that the autoimmune mechanism is involved in the pathogenesis of most cases of CU. However, there are patients where the autoimmune response can not be argued. Therefore, other possible etiopathogenic factors, as discussed above, must be taken into account. The inflammatory response encountered in our CU cases is a mixed Th1/Th2/Th17 type, partly correlated with certain abnormal laboratory test values and with autologous serum skin test.

In addition to blocking the effect of histamines, second-generation H1 antihistamines also have anti-inflammatory properties. This effect was demonstrated by in vitro studies (Leurs et al 2002), but promising results were only later confirmed by in vivo studies at much higher doses than those commonly used in the treatment. The reduced values of the inflammatory cytokines studied, clinically validated by the drastic reduction or disappearance of symptoms in all patients, support the anti-inflammatory effect of the long-term treatment with anti-H1. Only IL-10 value, which is an inhibitory cytokine, did not vary under treatment with H1 antihistamines.

There are no data in the literature investigating the effect of Levocetirizine and Desloratadine on the cytokines involved in the pathogenesis of allergic inflammation in chronic urticaria. The efficiency of H1 antihistamines in chronic urticaria is first evaluated clinically, by inhibiting the emergence of urticarial lesions and itching (Church 2012) It is not absolutely necessary to correlate the clinical parameters with inflammatory parameters. This study provides a correlation of the clinical parameters and the response to treatment with the level of certain proinflammatory or anti-inflammatory cytokines involved in chronic urticaria. Such a complex evaluation is needed in the attempt to unravel the additional mechanisms of each antihistamine alone, in order to be able to choose the optimal medication in patients with chronic urticaria.

Desloratadine, an active metabolite of loratadine, is a potent anti-H1 drug with anti-allergic and anti-inflammatory properties, especially when used in higher doses. This effect has been confirmed by our study by reducing the level of pro-inflammatory interleukins under therapy.

Levocetirizine, an active enantiomer of cetirizine, more potent than this one, has favorable pharmacokinetic and pharmacodynamic characteristics, proving its ability to quickly reduce itching and onset of urticarial lesions in patients with CU. Moreover, it has anti-inflammatory effects, also observed in our study.

Regarding the changes in cytokine levels in the group of patients treated with Desloratadine, compared to those treated with Levocetirizine, there was a significantly greater decrease in IL-1β in patients treated with Desloratadine than in those treated with Levocetirizine. IL-1β is an interleukin playing an essential role in the immune response, stimulating LyT differentiation and activation. However, the reduced levels of other proinflamatory interleukins, IL-2, IFN-γ, TNF-α, IL-4, IL-17 and IL-31, were not significantly different between the two groups. The data obtained are slightly inconsistent with the literature. There are studies evaluating the effects of the two antihistamines on serum levels of proinflammatory cytokines in allergic rhinitis (Ciprandi et al 2005). Given that some studies have shown that Levocetirizine provides a better disease control than Desloratadine (Staevska et al 2010), Levocetirizine was expected to determine significantly more reduced proinflammatory cytokine levels than Desloratadine. These differences may be due to the small number of patients included in the study and to the heterogeneity of chronic urticaria. Extensive studies would be needed to evaluate the anti-inflammatory effect of antihistamines in different subtypes of chronic urticaria.

Conclusions

H1 antihistamines are able to control the symptoms of chronic urticaria in most cases. The recommended treatment in patients with CU should be individualized for each patient. H1 antihistamines significantly reduce plasma levels of IL-1β, IL-2, IL-4 IL-6, IFN-γ, TNF-α, IL-17 and IL-31, but not IL-10 levels. Patients treated with Desloratadine recorded a greater decrease in IL-1β than those treated with Levocetirizine. There are no differences between the two compounds in terms of their effects on other cytokines investigated.

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