Antioxidant and inflammatory status of Tunisian patients with chronic spontaneous urticaria and effect of Desloratadine: a case-control study

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ABSTRACT

Objective: The aim of our study is to investigate the antioxidant status, inflammatory parameters, hematologic markers, clinical data of CSU Tunisian patients and the effect of a first-line treatment of CSU, which is Desloratadine 5mg/day on these different parameters.
Methods: This study enrolled 30 CSU patients and 30 controls. We assessed antioxidant parameters (Total antioxidant status (TAS) and glutathione S-Transferase (GST)), inflammatory markers (Albumin, Alpha 1, alpha2, beta1 globulins and CRP) and hematologic numeration. We assessed the Urticaria Activity Score (UAS).
Results: Alpha1, alpha2, beta 1 globulins, CRP, Leucocytes and basophils were significantly increased in patients at baseline versus controls ($p<0.05$). TAS, GST activity and albumin were significantly decreased in patients at baseline versus controls ($p<0.05$). TAS and GST activity were significantly increased in patients after treatment versus patients before treatment ($p<0.001$). Alpha1, alpha2, beta 1 globulins, CRP, albumin, leucocytes and basophils were significantly decreased in patients after treatment versus patients before treatment ($p<0.05$). A significant correlation between CRP and UAS ($r=0.2$; $p<0.001$) was noted. UAS assessment highlighted the efficacy of 30 days-antihistaminic treatment.
Conclusion: Our study emphasizes the involvement of oxidative stress in CSU. Interestingly, we found that desloratadine exerted anti-inflammatory and antioxidant effects.

KEY WORDS: Chronic spontaneous urticaria, Oxidative Stress, Inflammation, Desloratadine

Introduction

Chronic spontaneous (idiopathic) urticaria (CSU) is a common dermatological condition defined as the occurrence of daily or almost daily wheals and pruritus for at least 6 weeks [1]. Despite the extensive search for underlying causes or triggering factors, the aetiology of chronic urticaria remains unclear in at least 80–90% of the patients; therefore, it is referred to as chronic spontaneous urticaria (CSU) [2]. CSU affects nearly 3% of the population in USA and Europe and accounts for nearly 75% of all chronic urticaria cases [3, 4] in both countries. CSU can significantly impair the quality of life [5]. Notably, CSU patients report symptoms that may last for several years [6]. This condition has been associated with significant psychosocial and physical impairment; resulting in substantial disability and diminished productivity. Patients report emotional distress, social isolation and lethargy [7]. The majority of skin irritants trigger reactive oxidant species generation through metabolic pathways activation [8]. Previous studies showed a systemic imbalance establishment between pro-oxidant compounds and antioxidant capacities in patients with CSU [9].

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Besides inflammation in CSU, patient's consequent to mast cell degranulation may lead to an increased oxidant stress status and decreased antioxidant capacities [10]. Therefore,

oxidant stress may have a bidirectional role in CSU onset and aggravation. Numerous factors, including mast cell activation, increased vascular permeability mediators release, lead to wheals appearance. Histamine is the most known mediator. Its role in the pathophysiology of CSU is well established [11]. Antihistamines are the first-line treatment for CSU. Desloratadine is a selective H_1-receptor antagonist with a favorable pharmacokinetic profile [12] and proven efficacy in randomized, controlled clinical trials [13]. Current practice guidelines for management of CSU describe an approach with non-sedating H_1 oral antihistamines as the initial agents. Besides, it has been demonstrated that desloratadine has an antioxidant activity *in vitro* [14]. In this context, we attended to investigate the effect of desloratadine 5mg once a day during 30 days on antioxidant status, inflammatory parameters, hematologic parameters and clinical data in CSU patients.

Materials and methods

Population study

This cross-sectional study included 30 patients of CSU attending the dermatology outpatient department of the Fattouma Bourguiba hospital of Monastir in Tunisia over a period of one year from July 2013 to November 2014. Written informed consent was obtained from all patients. The study protocol, patient information sheet and consent form were approved by the Institutional Ethics Committee.

A detailed history and clinical examination was recorded for each patient. The diagnosis is defined as urticarial skin lesions, occurring intermittently or continuously for more than 6 weeks. We excluded from this study patients having any subtype of CU (physical and cholinergic urticarias, urticarial vasculitis, hereditary angio-oedema: inducible urticaria) and those receiving immunosuppressive therapy for the last four weeks. Patients were disrupted from H_1 and H_2 antihistamines for 10 days prior to the study. They were given desloratadine 5 mg/day for 30 days. We assessed a first check up before treatment and a second one after one month of treatment. Venous blood was drawn into simple, EDTA and heparin of lithium tubes. Whole blood was separated by centrifugation (4000 rpm, 10 min at 4°C). The samples were separated and stored at -20 °C until use. EDTA serum aliquots were objected to hematologic measurements. Heparin of lithium serum aliquots were objected to TAS evaluation. Simple tube serum aliquots were employed to GST activity and protein electrophoresis.

Clinical and biological study

Urticaria Activity Score

Urticaria Activity Score (UAS) is frequently used in routine clinical practice to evaluate chronic urticarial severity and treatment efficacy. The EAACI/GA2LEN/EDF/WAO guideline recommends the use of a straightforward and well established symptom UAS [15]. Its values depend on the number of wheals (0–3 points) and the intensity of pruritus (0–3 points). In this study, UAS was assessed according to the mean number of wheals and severity of itching, which had appeared during a week before blood sampling. We estimated UAS for CSU patients before and after desloratadine 5mg/day for 30 days of treatment.

Total antioxidant status

Total antioxidant stress (TAS) of heparinized plasma was measured using colorimetric method, which is based on the bleaching of the characteristic color of a more stable ABTS [2,2′-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid)] radical action by antioxidants. TAS concentrations were performed using commercials tests manufactured by Randox Laboratories (UK, Antrium).

Gluthatione-S-transferase activity

Gluthatione S-transferase (GST) activity of heparinized plasma was determined using spectrophotometer following the method of Habig et al. [16]. 1mM 1-chloro-2,4-dinitrobenzene (CDNB) was added to a potassium phosphate buffer pH 7.5 containing 1 mM GSH 1% absolute ethanol, the change in absorbance at 340 nm was measured as a function of time. Results were expressed as µM of GSH-CDNB conjugate formed/min/ml.

Inflammatory proteins measure

Albumin, alpha 1, alpha 2 and beta 1 globulins were determined in the serum by capillary electrophoresis on Konélab 20i ™ (Thermo Electron Corporation) and were analysed using a software Capillarys ™ (Sebia). CRP was measured

using an immunoturbidimetric method (Konélab 30™).

Hematology quantifications

Hematologic parameters were measured by Beckman Coulter, Coulter GENS and Coulter LH 750 Analyzers.

Statistical analysis

SPSS version 20.0 was used to explore our results. Student's t-test and Correlation test were used for Means comparison test. Odds ratios and their 95% confidence interval (CI) were determined. $p<0.05$ was considered statistically significant.

Results

Our study rolled 30 CSU patients and 30 controls, age and gender matched. Patients' mean age was 36.9 ± 12.32 years ranging from 20 to 60 years. Controls mean age was 36.1 ± 10.48 years ranging from 21 to 56 years. Table (1) summarizes our study population features.

Table 1. Study population features

Characteristics	Patients (n=30)	Controls (n=30)
Age (mean ± SD)	36.9 ± 12.32	36.1 ± 10.48
Gender (male/female)	16 / 14	16 / 14
Duration of urticaria	2 months to 1 year	-
Presence of angi-oedema	80 %	-

UAS assessment highlighted the efficacy of 30 days - antihistaminic treatment by a 54.5% reduction in wheals sizes and by a 63.6% reduction in itching severity - Table (2). TAS, GST activity and albumin were significantly decreased in patients at baseline compared to controls ($p<0.05$) Table (3). Alpha1, alpha2, beta1 globulins and CRP were significantly increased in patients at baseline compared to controls ($p<0.05$). TAS and GST activity were significantly increased in patients after treatment compared to patients before treatment ($p<0.001$).

Table 2. Urticaria Activity Score (UAS)

		CSU patients (n=30)		Symptoms reduction (%)
Symptoms	**Score**	**SBT (%)**	**SAT (%)**	
Wheals appearing during the last 24 h	**0**	0	27.27	Size of hives after 30 days of treatment 54.5
	1	36.36	31.82	
	2	18.18	13.64	
	3	45.45	27.27	
Severity of the itching during the last 24 h	**0**	0	31.82	Itching after 30 days of treatment 63.6
	1	18.18	9.09	
	2	36.36	36.36	
	3	45.45	22.73	

SAT: Scoring after treatment, **SBT:** Scoring before treatment, **(a)** 0= None, 1=Mild(<20 wheals /24h), 2=Moderate(20-50 wheals/24h), 3=Intense (>50 wheals/24h), **(b)** 0= None, 1=Mild(not annoying), 2=Moderate(troublesome but does not interfere with normal daily activity or sleep)), 3=Intense (Severe itch, sufficiently troublesome to interfere with normal daily activity or sleep).

Alpha1, alpha2, beta1 globulins, CRP and albumin were significantly decreased in patients after treatment compared to patients before treatment ($p< 0.001$). Leucocytes and basophils were significantly increased in CSU patients before treatment compared to controls ($p<0.05$) Table (4). Leucocytes and basophils were significantly decreased in CSU patients after treatment compared to those before treatment ($p<0.05$). However, neutrophils, lymphocytes, monocytes, eosinophils, hemoglobin and platelets showed no significant differences between different groups. We found a significant correlation between CRP and UAS ($r=0.2$; $p<0.001$). Unfortunately, no significant correlation between antioxidant parameters and UAS was revealed despite patient's remission.

Table 3. Antioxidant and inflammatory results in CSU patients before and after Desloratadine treatment compared to controls

Proteins	Patients n=30		Controls n=30	*p*-values
	BT	AT		
TAS (mmol/l)	1.88 ± 1.13	2.44 ± 0.44	2 ± 0.1	$p_1 = 10^{-6}, p_2 = 0.001, p_3 = 0.01$
GST (UI/ml)	17.23 ± 6.13	27.73 ± 8.81	20 ± 0.1	$p_1 = 10^{-6}, p_2 = 0.003, p_3 = 10^{-6}$
Albumin (g/l)	38.86 ± 1.83	36.98 ± 2.05	42.35 ± 4.23	$p_1 = 10^{-6}, p_2 = 0.002, p_3 = 3.\ 10^{-5}$
Alpha1 Globulin (g/l)	3.37 ± 0.60	2.90 ± 0.42	2.20 ± 0.51	$p_1 = 7.\ 10^{-5}, p_2 = 7.\ 10^{-5}, p_3 = 10^{-6}$
Alpha2 Globulin (g/l)	7.55 ± 1.09	7.16 ± 1.10	5.98 ± 1.16	$p_1 = 0.001, p_2 = 7.\ 10^{-5}, p_3 = 4.\ 10^{-5}$
Beta1 Globulin (g/l)	4.72 ± 0.57	4.34 ± 0.54	7.43 ± 1.26	$p_1 = 10^{-6}, p_2 = 10^{-6}, p_3 = 10^{-6}$
CRP (mg/l)	4.42 ± 1.30	3.45 ± 1.17	1.89 ± 1.32	$p_1 = 3.\ 10^{-5}, p_2 = 0.328, p_3 = 0.074$

Values are presented as mean ± standard deviation. CSU: chronic spontaneous urticaria, DCL: Desloratadine, TAS: Total Antioxidant Status, GST: glutathione S-Transferase, CRP: C-reactive protein. Confidence interval (CI) was taken as 95%, $p < 0.05$ values were accepted as statistically significant. Results are provided as mean ± standard deviation. BT: Before treatment; AT: After treatment.p1 : p-value between before and after treatment , p2 : p-value between controls and before treatment, p3 : p-value between controls and after treatment

Table 4. Hematological parameters levels of CSU patients before and after Desloratadine treatment compared to controls

Proteins	Patients n=30		Controls n=30	*p*-values
	BT	AT		
Leucocytes(10^3/mm^3)	8.10 ± 2.20	7.73 ± 1.70	6.41 ± 1.80	$\mathbf{p_1 = 0.048, p_2 = 0.021, p_3 = 0.032}$
Neutrophils(10^3/mm^3)	5.26 ±1.4	5.02 ± 1.1	4.16 ± 1.2	$p_1 = 0.512, p_2 = 0.05, p_3 = 0.11$
Lymphocytes(10^3/mm^3)	2.18 ± 0.5	2.08 ± 0.45	1.73 ± 0.48	$p_1 = 0.411, p_2 = 0.055, p_3 = 0.07$
Monocytes(10^3/mm^3)	0.4 ± 0.11	0.38 ± 0.08	0.32 ± 0.09	$p_1 = 0.532, p_2 = 0.071, p_3 = 0.08$
Eosinophils(10^3/mm^3)	0.2 ± 0.05	0.19 ± 0.04	0.16 ± 0.04	$p_1 = 0.611, p_2 = 0.06, p_3 = 0.07$
Basophils(10^3/mm^3)	0.04 ± 0.01	0.03 ± 0.01	0.03 ± 0.009	$\mathbf{p_1 = 0.04}, \mathbf{p_2 = 0.035}, p_3 = 0.06$
Hb (g/dL)	12.66 ± 0.80	12.32 ± 1.17	12,68 ± 0,30	$p_1 = 0.196, p_2 = 0.925, p_3 = 0.23$
Platelets (10^3/ mm^3)	214.58 ± 35.51	201.87 ± 20.57	380 ± 84.27	$p_1 = 0.086, p_2 = 0.137, p_3 = 0.09$

Values are presented as mean ± standard deviation. CSU: chronic spontaneous urticaria, DCL: Desloratadine, Hb: Hemoglobin. Confidence interval (CI) was taken as 95%, $p < 0.05$ values were accepted as statistically significant. Results are provided as mean ± standard deviation.

Discussion

In this study, patients' ages ranged from 20 to 60 years. Literature cites that CSU occurs across all age groups largely in young women between 20 and 40 years of age [7].

Previous studies found that the current standard of care, H_1-antihistamines at licensed doses, is only effective at resolving symptoms in less than 50 % of patients with CSU [17]. According to these studies, further increase in H_1-antihistamines doses did not improve treatment response [18]. Antihistamines guidelines recommend the addition of a third-line treatment option of omalizumab, ciclosporin or montelukast [19]. One of the most important aspects of this study is the assessment of UAS in order to appraise disease remission and patient's quality of life after desloratadine 5 mg daily treatment. UAS assessment highlighted the efficacy of 30 day-antihistaminic treatments by a 54.5% reduction in wheals sizes and by a 63.6% reduction in itching severity. However, UAS is largely criticized since it relies on subjective description and may not be so accurate and quantitative [20]. The relevant decreased TAS level and GST activity level in patients at baseline compared to controls may suggest the involvement of oxidative stress in the pathogenesis of CSU. The diminished antioxidant findings at baseline are likely to be a consequence of a prolonged reactive oxygen species generation due to chronic inflammation. Previous findings suggest the involvement of oxidative stress in the pathogenesis of CSU [21, 22]. In this study, antioxidant capacities increased parallel to remission evaluated by UAS. However, no significant correlation between both parameters was observed. This may show that

desloratadine exerts anti-inflammatory effects that attenuate oxidant reactions. Desloratadine antioxidant capacities ought not due to its formula, which contains two conjugated cycles. Cassano et al. showed that hydrogen peroxide (H_2O_2), oxidant molecule and superoxide dismutase, antioxidant enzyme were significantly elevated in patients with CSU before desloratadine treatment as compared with control subjects. Their findings conducted that treatment with desloratadine caused a relevant reduction of radical oxygen species generation and superoxide dismutase activity [23]. This study was performed to evaluate the effect of desloratadine on positive inflammatory proteins (alpha1, alpha2, beta1 globulins and CRP). The relevant increase, which we found, of alpha1, alpha 2, beta1 globulins and CRP in CSU patients at baseline indicated inflammatory events booting the disease burden. CRP is a potent activator of the classical cascade of complement and in this way, may initiate or exacerbate the inflammatory lesions. In this study, we noted significant reduction of inflammatory markers (alpha1, alpha2, beta1 globulins and CRP) in CSU patients after treatment associated with patients' health improvement. We also found a linear correlation between CRP and UAS in patients. This finding is an additional emphasis of CRP's role as a relevant parameter in clinical CSU assessment. Similar results were found by Ohtsuka [24]. The latter established an elevated CRP levels in CSU patients before the start of therapy [24]. The same study ascertained that CSU patients with elevated sensitivity-CRP showed better response to oral cyclosporine therapy than CSU patients with decreased sensitivity-CRP [24]. A current study showed that plasma fibrin degradation products, d-dimer and CRP markers of patients with chronic urticaria were well correlated with each other and significantly associated with disease severity [25]. Levels of all these parameters reduced as their disease condition improved, while they increased when the disease became aggravated [25]. In our study, a statistically significant decrease of albumin was observed in CSU patients after treatment ($p<0.001$). Our study confirmed previous findings that indicated significantly lower albumin and significantly higher CRP were achieved in CSU patients than controls [26]. In our study, Leucocytes and basophils were increased in CSU patients at baseline then decreased after treatment. Ohtsuka found that leukocytes and basophils counts in elevated high sensitivity-CRP patients were significantly increased than those in patients showing no elevation of high sensitivity-CRP [24]. A previous study suggested that CSU could be identified as a mast cell- and basophil-dependent inflammatory disorder of the skin accompanied by acute phase response [27]. Further to literature, CSU onset is initiated by inappropriate activation and degranulation of dermal mast cells. The latter progress to a complex pool of varied proinflammatory cytokines release and inflammatory mechanisms such as cellular infiltration evolving into lymphocyte and granulocyte. These cells, in turn, release more proinflammatory mediators that recruit and activate other cell types such as leucocytes and basophils, thereby amplifying and extending the cell response [11]. Unexpectedly, we found that platelets number was reduced in patients before and after treatment compared to controls. In fact, platelets are activated during inflammatory processes and are involved in modulating inflammatory and immune response via various mediator releases. Kasperska-Zajac et al. found that in contrast to CSU, chronic urticaria patients with a positive response to autologous serum skin testing associated with increased secretion of platelet chemokines [28]. In conclusion, Desloratadine was associated with clinically relevant decreases in severity of hives and associated pruritus, as well as meaningful improvement on quality of life. Interestingly we investigate that Deslaratadine exerted antioxidant and anti-inflammatory properties on CSU Tunisian patients.

Conflict of Interest

We declare that we have no conflict of interest.

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