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ORIGINAL ARTICLE

Turkish dermatologists' approach for chronic spontaneous urticaria: A questionnaire based study

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ABSTRACT

Background/Objectives: Chronic spontaneous urticaria (CSU) is a common skin disorder which represents a challenge both for the patients and physicians. Guidelines and treatment algorithms have been created to help physicians to ease management. Our aim was to determine Turkish dermatologists' approach to CSU with regard to treatment, search for causative factors and use of instruments to assess the quality of life and severity of the disease.

Methods: This was a cross-sectional methodological study which was performed by delivery of a questionnaire including ten questions about the management of CSU.

Results: Analyses of 314 questionnaires revealed that the most common first-line treatments were non-sedating antihistamines in standard doses (65.6%), while second-line treatment was updosing antihistamines (59.9%) followed by addition of sedative-antihistamines (26.4%) and systemic steroids (19.1%). Third-line treatment option was omalizumab in 35% followed by systemic steroids. Twenty-two percent of the dermatologists referred the patients to a center experienced in urticaria. Most of them were performing laboratory testing for underlying causes including thyroid function tests, C-reactive protein, thyroid auto-antibodies, stool analyses, infection markers. Urticaria activity score and chronic urticaria quality of life questionnaire were used by 30 and 13%, respectively, while 56% were using none of the instruments.

Conclusion: Our study showed that the therapeutic management of Turkish dermatologists was parallel to the European Urticaria Guidelines. The high utility of omalizumab as a third line regimen improved patient care. Nevertheless there is a need for centers experienced in urticaria to refer antihistamine-resistant patients where third-line treatment options can not be implemented.

Introduction

Chronic spontaneous urticaria (CSU), is a skin disorder characterized by recurrent, transient and itchy wheals and/or angioedema present for more than 6 weeks, due to a known or unknown cause.[1] CSU has a point prevalence of 0.5–1% in the total population and can be seen in all age groups but the peak incidence is between 20 and 40 years of age.[2] The disease generally lasts for 1–5 years but

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can be prolonged in severe cases, cases associated with angioedema, combination with physical urticaria or with a positive autologous serum skin test.[2,3] Most often, the cause cannot be identified easily but about 45% of CSU patients have autoantibodies against their own IgE or IgE receptors that lead to spontaneous wheals on the skin.[1,3,4] On the basis of recent data, the European Urticaria Guidelines from the European Academy of Allergy and Immunology (EAACI/GA^{2}LEN/EDF/WAO) only recommend diagnostic laboratory tests limited to differential blood count, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).[1] Additional diagnostic tests can be made according to the patients' history.[1] Curative treatment is not available for most of the patients since an underlying cause is rarely detected. Symptomatic treatment remains the mainstay of the therapy.[2]

Guidelines and treatment algorithms have been created to help the patients as well as their physicians.[2] EAACI/GA^{2}LEN/EDF/WAO guideline recommends using modern non-sedating H_1 antihistamines (nsAHs) for the first line treatment. If lesions persist after 2 weeks of treatment, increasing the dosage of modern nsAHs up to fourfold is recommended as the second line treatment. If lesions further persist for 1–4 weeks, the guidelines suggest to add omalizumab or cyclosporine-A (Cyc-A) or montelukast as third line treatments.[1,5–7]

In our study we investigated the Turkish dermatologists' approach to CSU patients; focusing on the medications prescribed as the first-line, second-line and third-line treatments, diagnostic testing for etiological factors and the scales used for activity and quality of life scoring.

Material and methods

A questionnaire including 10 questions was created to distribute to Turkish dermatology specialists in a national congress. It was also sent via e-mail to other dermatology specialists who could not attend to the congress. E-mail survey access was available for 2 months via SurveyMonkey.

The questions related to demographic information included number of years in practice, affiliation and total number of CSU patients examined in a month. The questions related to the management of CSU consisted of the preferred medications as first, second and third line, time for second visit, the rationale for choosing the third-line treatment medications, the laboratory tests ordered for investigation of CSU etiology and tools that are used for the assessment of urticaria activity and quality of life impairment. All responders were requested to fill out the questionnaire completely. Uncompleted questionnaires were excluded from the study. No payment was made for the responders.

The rationale for making this questionnaire was to gather information and create a basis for the generation of Turkish urticaria guideline. The results of the survey were also used for this purpose.

Statistical analyses

The data obtained from surveys were recorded and reviewed by using MS-EXCELL. The data were first analyzed descriptively. Then explorative comparative statistical analyses comparing the different practicing years, working places, treatment modalities and usage of laboratory tests were performed.

Results

In total, 314 questionnaires were available for statistical analyses. Most of the responders (51.9%) have been practicing as a dermatology specialist for 5–20 years, followed by 26.4% practicing for 0–5 years and 21.7% practicing for over 20 years, respectively. The majority of the responders (30.3%) were working at university hospitals, while remaining 27.7% at the government hospitals, 24.2% at private hospitals and 17.8% at training and research hospitals, respectively. Most of the specialists (32.2%) examined 5–10 CSU patients per month.

Standard doses of non-sedating antihistamines (nsAHs) (65.6%) were the most common first treatment of choice, followed by combination of sedating and nsAHs (12.7%) and updosing of nsAHs(12.1%) (Table 1). Updosing of nsAHs (11 responders), combination of sedating and nsAHs (18 responders) and systemic steroids (2 responders) were the three most preferred first line treatments by the dermatologists working at private hospitals. Eleven responders from university hospitals also preferred high dose nsAHs as the first line treatment.

Majority of the dermatologists (50.3%) evaluated their patients 2 weeks after the first visit. If the lesions were refractory after the first-line treatment, most of the dermatologists (59.9%) preferred to upload nsAH treatment dosage, while 83 (26.4%) added sedative anti-histamines (sAHs) to the preexisting treatment and 70 (22.3%) preferred combination treatment of two different nsAHs as the second-line treatment, respectively (Table 2).

If the lesions still persisted despite the second-line treatment, the responders preferred omalizumab (35%), systemic steroids (22.9%), referral to centers experienced in urticaria (22%) and Cyc-A (11.1%) as the third line, respectively. The reported reasons for preferring omalizumab were due to its effectiveness, safety and its existence in the latest guidelines, respectively. The responders preferred systemic steroids at the second rank because of its effectiveness, fast action and its existence as a conventional treatment, respectively. The third most commonly preferred treatment Cyc-A was reported to be an effective, guideline recommended and fastly acting option, respectively. The responders that preferred omalizumab at the third line were working at university hospitals (66), training and research hospitals (32), private hospitals (8) and government hospitals (4). The responders that preferred systemic steroids as the second most common third line treatment were working at government hospitals (33), private hospitals (21), university hospitals (9) and training and research hospitals (9). Cyc-A, the third most common third line treatment, was preferred by the responders who were working at private hospitals (13), university hospitals (9), government hospitals (8) and training and research hospitals (5). Some of the responders referred patients to centers experienced in urticaria when they were refractory to second line treatments. These responders were working at government

Table 1 The preferred first line treatment options for CSU.

What is your first-line treatment option in CSU?	N	%
Standard dose non-sedating antihistamines	206	65,6%
Updosing of non-sedating antihistamines	38	12,1%
Combination of two non-sedating antihistamines	31	9,9%
Sedating antihistamines alone	3	1,0%
Combination of sedating and non-sedating antihistamines	40	12,7%
Leukotriene antagonists alone	0	0,0%
Non-sedating antihistamines and leukotriene antagonists	3	1,0%
Non-sedating antihistamines and H_2 blockers	4	1,3%
Non-sedating antihistamines + H_2 blockers + leukotriene antagonists	1	0,3%
Mast-cell stabilizers alone	0	0,0%
Mast cell stabilizers + non-sedating antihistamines	7	2,2%
Systemic steroids	4	1,3%
Pseudoallergen low diet	22	7,0%
Others	8	2,5%

Most of the dermatologists preferred standard dose antihistamines as the first line treatment of CSU. This was followed by combination of sAHs and nsAHs. Updosing of nsAHs, combination of two nsAHs and low pseudoallergen diet were the other commonly preferred first-line treatments.

Table 2 The preferred second line treatment options for CSU.

If your patients' symptoms do not respond to first line treatment, what is your second line treatment option?	N	%
Switching the treatment to another non-sedating antihistamine	53	16,9%
Up dosing of non-sedating antihistamine alone	188	59,9%
Combination of two non-sedating antihistamines	70	22,3%
Adding sedating anti-histamine to previous treatment	83	26,4%
Adding sedating anti-histamine to previous treatment	15	4,8%
Leukotriene antagonists alone	1	0,3%
Non-sedating antihistamine and leukotriene antagonists	45	14,3%
Non-sedating antihistamine and H_2 blockers	30	9,6%
Non-sedating antihistamine + H_2 blockers + leukotriene antagonists	14	4,5%
Mast-cell stabilizers alone	1	0,3%
Mast cell stabilizer + non-sedating antihistamine	18	5,7%
Systemic steroids	60	19,1%
Doxepin alone	6	1,9%
Adding doxepin to previous treatment	12	3,8%

If the patients' symptoms do not relieve by the first line treatment, majority of the dermatologists (59.9%) prefer updosing of nsAHs. Also adding sAHs to the previous treatment (26.4%), combination of two nsAHs (22.3%) and systemic steroids (19.1%) are the other most common preferred second-line treatments despite they do not take place in the guideline. Beside those treatments, changing a nsAH to another (16.9%), combination of nsAHs and leukotriene antagonists (14.3%) and combination of nsAHs and H_2 antagonists (9.6%) are preferred alternative treatments that cannot be underestimated.

hospitals (34), private hospitals (28), training and research hospitals (5) and university hospitals (2), respectively.

Laboratory tests that commonly ordered for the investigation of etiological factors were; complete blood count (95.2%), thyroid function tests (82.2%), routine biochemical laboratory tests (77.7%), urine analysis (76.8%), sedimentation rate (74.5%), stool analysis for ova (73.6%) and CRP (73.2%), respectively. Testing for *Helicobacter pylori* (*H. pylori*) (36.6%) was higher than expected. Autologous serum skin test (ASST) has been performed mostly by university hospitals (46), training and research hospitals (18) and private hospitals (16), respectively. To find an underlying etiological cause of CSU, investigation of infectious focuses (57.6%) has been mostly ordered by university hospitals (55), followed by private hospitals (47) and government hospitals (46). Additionally, some responders (29.6%) consulted their patients to psychiatrists.

A majority of the responders (56.4%) do not evaluate CSU patients' disease activity or impact of disease on quality of life. Only 30.6% of the responders were using urticaria activity score (UAS) scale for the evaluation of urticaria severity. Most of the responders, who were using UAS scale, were practicing for 5–20 years (47) and majority of them were working at university hospitals (56), training and research hospitals (25), government hospitals (9) and private hospitals (6), respectively.

Discussion

The aim of treatment in chronic spontaneous urticaria is complete symptom control as well as providing relief for the quality of life impairment. Professional societies and clinical experts have prepared recommendations and guidelines for the diagnosis and management of chronic urticaria. Following treatment guidelines provides ease for the management of the diseases, nevertheless, insurance issues somewhat may limit the adherence to guidelines.

Review of Medline resulted in four studies concerning the approach of physicians to urticaria management. First of them was from Germany, second was from United Kingdom (UK), third was from Canada and the last one from France.[8–11] These studies mainly concentrated on the treatment approaches, diagnostic programs and awareness of guidelines. In our study, we set out that most of the Turkish dermatologists' preferred standard dose nsAHs for the first line of urticaria treatment (65.6%). For the second line, updosing of nsAHs treatment (59.9%) was the most common treatment of choice and for the third-line treatment, omalizumab (35%) was preferred mostly. In their study, Weller et al. found out that most of the physicians (46%) preferred standard dose nsAHs treatment for the first line.[8] In the UK study, all the dermatologists that participated recommended nsAHs as the first-line treatment.[9] Fexofenadine (45%) was the most commonly prescribed nsAH.[9] In the Canadian study, responders were asked for 'Which of the treatments have you tried for CSU?' Majority of them (96.83%) preferred H_1-AHs and the next most popular therapy was oral corticosteroids (63.49%). These were followed by montelukast (55.56%), Cyc-A (38.10%) and omalizumab (26.89%).[10]

We verified that combination of sAHs and nsAHs and updosing of nsAH treatments were the other most common choices in the first-line treatment of urticaria. Besides the standard dose of nsAH treatment, updosing of nsAHs, sAH and oral steroids were also used by the physicians as the first line treatment option in Weller's study.[8]

Most of the Turkish dermatologists examined their patients 2 weeks after the first visit, as recommended by the EAACI/GA^{2}LEN/EDF/WAO guideline. If the urticaria was refractory to the first-line treatment, majority of the Turkish dermatologists preferred to updose nsAHs (59.9%) in the second-line treatment, same as the recommendation of the EAACI/GA^{2}LEN/EDF/WAO guideline 2013. This was followed by adding sAHs to the previous treatment (26.4%), combination of two nsAHs (22.3%), systemic steroids (19.1%), switching to another nsAH (16.9%), combination of nsAHs and leukotriene antagonists (14.3%), pseudo allergen low diet (10.8%) and combination of nsAHs and H_2 blockers (9.6%), respectively.

In Weller's study, most commonly preferred second line treatment for the refractory patients was systemic steroids (27.2%).[8] Also high-dose of nsAHs (25.4%), sAHs (22.6%) (alone or in combination) and switching first-line nsAH to another one (15.3%) were preferred in the treatment of the refractory patients, respectively.[8] In the Canadian study, oral steroids (26.32%) were the most commonly preferred second-line treatment. This was followed by omalizumab (24.56%), Cyc-A (19.30%), H_2 antihistamines (16.28%) and montelukast (6.98%), respectively.[10]

In the UK group, if the patients were resistant to first-line nsAH treatment, before updosing of nsAH, dermatologists generally preferred additional second-generation nsAH (75.8%) and combination of second generation nsAHs (42.6%).[9] If the second-generation nsAH treatments have failed, they preferred H_2 blockers (43.3%), leukotriene receptor antagonists (LTRA) (25%), sAHs (18.3%) and Cyc-A (6.7%) respectively.[9] None of the participants preferred corticosteroids if the nsAH have failed.[9] Different treatment approach of the UK group may be due to following the British Society for Allergy and Clinical Immunology (BSACI) and British Association of Dermatology (BAD) guidelines rather than EAACI/GA^{2}LEN/EDF/WAO guidelines.

In our survey, omalizumab (35%) was the most commonly preferred third-line treatment. This was followed by systemic steroids (22.9%), consulting patients to an experienced urticaria center (22%) and Cyc-A (11.1%), respectively. The low preference of Cyc-A can be related to recent introduction of omalizumab to the treatment algorithm of CSU. Due to its side effects and need for frequent laboratory tests during treatment, the place of Cyc-A in CSU treatment seems to be replaced by omalizumab. When the reasons for treatment choices were evaluated, omalizumab was reported to be fast in action, efficacious, and safe.

In our study, systemic steroids were commonly preferred by the dermatologists who were working at government hospitals and private hospitals. The responders reported that they preferred

systemic steroids because it is an effective, rapid acting and conventional treatment. Likewise, Cyc-A was also preferred mostly by dermatologists working in private hospitals due to its effectiveness, being a treatment recommended by the guidelines and its rapid action. Because the dermatologists working in private hospitals and government hospitals have limited access to omalizumab treatment due to reimbursement issues, systemic steroids and Cyc-A still constitute major treatment choices in these institutions. But in these centers, most of the dermatologists preferred referring those AH-resistant patients to centers experienced in urticaria instead of starting third line treatments. This emphasizes the need for qualified centers experienced in urticaria as a referral center which shall be reached via networks of physicians.

In the tertiary centers like university/training/research hospitals, omalizumab was the most commonly preferred third-line treatment of urticaria. Since these hospitals had no limitation to prescribe omalizumab, systemic steroids and Cyc-A was less commonly preferred by these centers.

Our study is different from the published ones since it evaluated the therapeutic approaches after the introduction of omalizumab to CSU management mainly after March 2014. We realized that after the introduction of omalizumab, the use of systemic steroids was substantially decreased; it remained to be preferred by the dermatologists who have no access to omalizumab therapy.

In the management of CSU, it is hard to identify the triggers because of the endogenous nature of the disease which makes it a challenging disease.[12] To identify the underlying causes of CSU, EAACI/GA^{2}LEN/EDF/WAO guideline recommends some laboratory tests as mentioned above. In our study, complete blood count (95.2%) was the most ordered laboratory test. It was followed by thyroid function tests (82.2%), routine biochemical tests (77.7%), urine analysis (76.8%), ESR (74.5%), stool analysis for ova (73.6%) and CRP (73.2%) respectively. Recommended basic tests as well as the extended laboratory programs were performed which might not at the end result in finding a relevant cause. In Weller's study, the three most common laboratory tests ordered were allergy tests (84.5%), differential blood count (82.3%) and total IgE values (81.4%).[8] The frequency of CRP/ESR testing was similar to our study. In Germany, allergy is linked to dermatology, so this could explain why allergy tests were performed in a high percentage.[9] In our survey, skin prick test (SPT) (18.2%), ASST (29.3%), total IgE (60.2%) and specific IgE (11.1%) were performed, respectively. There was a strikingly low incidence of search for allergic causes in the Turkish dermatologist group which points to a high level of knowledge that chronic urticaria is not an allergic disease. Search for underlying infectious agents such as consultation of an ear–nose–throat specialist (77.6%) and a dentist (77.3%) was higher in the German study than our study (57.6%).

In the UK study group, the most ordered laboratory test was full blood count (73.5%), followed by examination of infectious focuses (61.3%), thyroid stimulating hormone (TSH) (49%) and thyroid function tests (46.9%). SPT was performed by only 2% of the dermatologists and none of them performed ASST.[9]

In the Canadian study, same as our study and UK study, most common diagnostic laboratory test was complete blood count (CBC) (82.52%).[10] Thyroid function tests and autoantibodies (74.6%), ESR (63.49%) and CRP (49.21%) were the other most common tests.[10] Overall (including our results), most commonly performed laboratory tests were found as CBC, thyroid hormones and thyroid autoantibody tests, examination of infectious focuses, ESR and CRP. In our study (74.5%), in UK study (42.9%) and in Canadian study (63.49%) ESR was more commonly used than CRP.

Although autoreactivity has been suggested to be the cause of almost half of the CSU cases,[13] the rate of performing ASST was found low in our study and other studies discussed above. The reasons for this might be that the test is a time consuming procedure with a high rate of false positivity in some studies and result of the test does not contribute much to the treatment approach.[14] Despite these limitations, its low cost and practicability makes it a useful screening tool. In the EAACI/GA^{2}LEN/EDF/WAO guideline, it is recommended to be performed in the extended programme.[1]

CSU patients frequently exhibit psychiatric comorbidities such as anxiety, depression and somatoform disorders. But the casual relationship is not identified. Whether these disorders act as a trigger or appear during the progress of this chronic disease remains to be determined.[15–17] Investigation of psychiatric diseases is not a basic recommendation in the EAACI/GA^{2}LEN/EDF/WAO guideline, but in our study, 29.6% of the responders directed their patients for a psychiatry consultation. The studies stated above did not mention psychiatry consultation, but given the frequent occurrence of psychiatric disorders in CSU patients, we suggest that this is a must step and should not be omitted in the CSU patient management.

H. pylori has been implicated in the pathogenesis of CSU and in a recent meta-analysis, it has been associated with a significant but weak risk of CSU.[18] In the EAACI/GA^{2}LEN/EDF/WAO guideline, for resistant urticaria patients, investigation of *H. pylori* was recommended. Testing for *H. pylori* was preferred in 36.6% of our responders, while in the German study; it was 29.1% and UK study 8.2%.

We noted that there were differences regarding treatment and evaluation of patients between tertiary and secondary centers. For instance performing ASST and search for infectious causes were more common in tertiary centers than secondary centers and implementation of omalizumab was more common in tertiary centers, which could be explained by time constraints and limitations of the insurance system.

Conclusion

Our study showed that there are different approaches in the management of CSU but the majority of Turkish dermatologists manage CSU patients parallel to the European guidelines, such as starting with nsAHs, updosing AHs and introducing omalizumab as the third step. The diagnostic approach was also similar to the European guideline, but extensive laboratory testing was performed for the purpose of finding an underlying cause. The main purpose of performing this study was to evaluate the therapeutic, diagnostic approaches of Turkish dermatologist' to CSU patients focusing on local expertise and needs and to further generate a base for the creation of Turkish urticaria guideline. The need for a concise and understandable guideline became apparent after this survey and the Turkish guideline has just been published.[19]

Limitations

This is a physician based survey study carried out on a voluntary basis. Therefore, dermatologists interested in this subject or practicing in academic settings were more prone to take the survey, and a selection bias is likely to occur. This may affect the generalizability of our results to the general dermatologist population. Our study was performed in 314 physicians who were specialized in dermatology. This constitutes approximately 20% of the 1520 dermatologists in Turkey. To generalize the results to all dermatologists in Turkey might also cause a bias.

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