Original Investigation
Orijinal Araştırma

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Evaluation of the treatment responses with the recommended tools in patients with symptomatic dermographism

Semptomatik dermografizmli hastalardaki tedavi yanıtlarının önerilen ölçeklerle değerlendirilmesi

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Abstract

Background and Design: Symptomatic dermographism (SD) is the most common form of the inducible urticaria that impairs quality of life significantly and requires further treatment. Guidelines recommend a stepwise approach starting with second-generation (sg) H1 antihistamines (AHs), and it has been advised that the same algorithm that is available for chronic spontaneous urticaria might be implemented in chronic inducible urticarias. However, there is a lack of clinical trials assessing the efficacy of AHs and omalizumab in patients with SD. In this study, we aimed to evaluate treatment responses in SD patients by using patient-reported outcomes and physician's assessment tools.
Materials and Methods: This prospective observational study included 58 patients with SD. Treatment responses were evaluated with urticaria control test (UCT), patient's global assessment of disease severity (PatGA-VAS), physician's global assessment of disease control (PhyGA-VAS), and dermatology quality of life index (DLQI) at 0, 4, 8, 12 and 24th weeks of the treatment.
Results: Fifty-eight patients (40 women and 18 men) with a mean age of 36.9±12.38 years (range: 17-72) were included in the study. The mean disease duration of the patients was 31.8±46.22 months. Fifteen patients (43.1%) responded to single-dose sg-AHs, while 25 (43.1%) responded to updosing or combination of sg-AHs. The response was confirmed by increased UCT scores, PhyGA-VAS ($p<0.001$), and decreased DLQI scores and PatGA-VAS ($p<0.001$). Eighteen patients were diagnosed as AH-resistant, and omalizumab was implemented. Total response rates increased to 86.2% at week 24 supplementation with omalizumab treatment.
Conclusion: One-third of SD patients is resistant to AHs and might require third-line treatment such as omalizumab.
Keywords: Inducible urticaria, omalizumab, symptomatic dermographism, urticaria control test

Öz

Amaç: Kronik indüklenebilir ürtiker'in en sık rastlanan tipi olan semptomatik dermografizm (SD), hastaların yaşam kalitesini önemli ölçüde etkileyen ve yine hastaların önemli bir bölümünde ileri tedavi yaklaşımları gerektiren bir hastalıktır. Tedaviye ikinci kuşak (İK) H1 antihistamin (AH) ile başlanması ve kronik spontan ürtikerdeki algoritmanın uygulanması önerilmektedir. Ancak AH'lerin ve omalizumabın SD'deki etkinliğini değerlendiren az sayıda klinik çalışma vardır. Bu çalışmada, SD'li olgulardaki tedavi yanıtları, hasta ve hekim değerlendirme ölçütleri kullanılarak ortaya konulmaya çalışılmıştır.
Gereç ve Yöntem: Bu prospektif gözlemsel çalışma, SD'si olan elli sekiz hastayı içermektedir. Tedavi yanıtları 0., 4., 8., 12. ve 24. haftalarda ürtiker kontrol testi (ÜKT), hastanın global hastalık şiddeti değerlendirmesi, hekimin hastalık kontrolünü global değerlendirmesi ve dermatoloji yaşam kalitesi indeksi (DYKİ) ile değerlendirildi.
Bulgular: Çalışmaya yaş ortalaması 36,9±12,38 (17-72) olan elli sekiz hasta (40 kadın ve 18 erkek) dahil edildi. Hastaların ortalama hastalık süresi 31,8±46,22 ay idi. Hastaların 15'i (%43,1) tek doz İK-AH'lere yanıt verirken, 25'i (%43,1), İK-AH'lerin doz artırımına veya kombinasyonuna yanıt verdi. Tedavi cevapları artmış ÜKT skorları, hekimin hastalık kontrolünü global değerlendirmesi ($p<0,001$) ve azalmış DYKİ skorları ile azalmış hastanın global hastalık şiddeti değerlendirmesi ($p<0,001$) ile doğrulandı. On sekiz hasta AH'lere dirençli olarak saptandı ve bu hastalara omalizumab tedavisi uygulandı. Hastaların omalizumab tedavisi ile toplam yanıt oranları 24. haftada %86,2'ye yükseldi.
Sonuç: SD hastalarının üçte biri AH'lere dirençli olup, omalizumab gibi üçüncü basamak tedaviler gerektirebilmektedir.
Anahtar Kelimeler: İndüklenebilir ürtiker, omalizumab, semptomatik dermografizm, ürtiker kontrol testi

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Introduction

Symptomatic dermographism (SD) is the most common form of the inducible urticaria (dermographic urticaria, urticaria factitia) which is presented by itching and/or burning skin sensations with itchy wheals following to scratching, rubbing, and/or scrubbing[1,2]. SD should be distinguished from the simple dermographism which is wealing with no itching in response to firm stroking of the skin[1,2]. The duration of the disease is 6.5 years, and disease has a very high impact on quality of life (QoL)[1,3,4]. The diagnosis can be made according to the patient's history and confirmation of provocation testing[2,5]. Treatment includes pharmacological treatment in addition to the trigger avoidance[1]. Guidelines recommend to start with a standard dose of a second generation (sg) H1-antihistamines (AHs), followed by up to four-fold increasing the sg-AHs in patient who is refractory to standard doses[1,6,7]. Higher than standard doses are usually required but some patients are also refractory to updosing of AHs[5]. In the latest European Academy of Allergology and Clinical Immunology 2017 guideline, only third line treatment is omalizumab[6]. Omalizumab is approved for chronic spontaneous urticaria (CSU) and highly effective in AH-refractory cases with CSU[8,9]. But omalizumab is still off-label for SD and there is a lack of clinical trials evaluating the treatment responses of omalizumab in patients with SD except for a recent placebo controlled trial performed by Maurer et al.[4]

Here, we aimed to assess treatment responses in SD patients by using patient-reported outcomes and physician's assessment tools.

Materials and Methods

This prospective study included fifty-eight patients with SD. Patients above 17 years old who were referred to our Urticaria Centers of Reference and Excellence (UCARE) center[10] were included in the study. Fric test 4.0 (Moxie, Berlin, Germany)[11] was performed as confirmatory test. Age, gender and disease duration were noted as demographic characteristics. This study was approved by İstanbul Okmeydanı Training and Research Hospital Institutional Review Board (approval number: 525, 48670771-514) and was conducted according to the principles of the Declaration of Helsinki. All participants provided written informed consent.

Stepwise treatment approach starting with standard dose AHs followed by updosing or combination of sg-H1-AHs and supplementation of omalizumab to AHs to non-responders was administered to all patients. Patient's global assessment of disease severity (PatGA-VAS), physician's global assessment of disease control (PhyGA-VAS), urticaria control test (UCT), and dermatology quality of life index (DLQI) were evaluated at weeks 0, 4, 8, 12 and 24. Treatment was directed prospectively due to the UCT scores and patients with UCT scores of ≥12 and <12 were regarded as responders and non-responders, respectively. The UCT and DLQI was applied to all patients[12,13]. UCT has 4 questions and each has 5 answers (0-4 points). Total score is the sum of all item scores (0-16 points) and a score of ≥12 indicates well controlled urticaria[14]. Pat GA-VAS is a 10 cm line to assess strength of patient complaints "no complaints" (0 cm) - "maximal complaints" (10 cm) while PhyGA-VAS is a 10-cm line ["not at all under control" (0 cm) - "completely under control" (10 cm)] to assess the disease control[14].

Statistical Analysis

SPSS software version 22.0 was used for statistical analyses. All numerical variables were reported as minimum, maximum, median, mean ± standard deviation, and percentages. Wilcoxon signed rank test was applied to measure the levels of significance values for differences in the mean UCT, DLQI and PhyGA-VAS, PatGA-VAS. Statistical significance was achieved at $p<0.01$. Non-parametric methods were performed.

Results

Demographic data of patients with symptomatic dermographism

The 58 patients with SD [40 women (69%) and 18 men (31%)] included in the study. The mean age and mean disease duration was 36.9±12.38 years (range: 17-72), and 31.8±46.22 months (range: 2-240 months) respectively.

Total response rates of the patients

Patients were evaluated at referral, 15 of the patients (25.9%) responded to single dose of sg-H1-AHs (UCT ≥12) while 25 (43.1%) responded to updosing or combination of sg-AHs. With the second line treatment approach, the number of responders were increased to 40 which corresponded to a total response rate of 69%. The remaining 18 patients were refractory to AHs but only 12 of them accepted third line treatment with omalizumab (150 mg every 2 weeks or 300 mg every 4 weeks). Total response rate increased to 81% (n=47) at week 4 of the omalizumab, to 84.5% (n=49) at week 12 and 86.2% (n=50) at week 24 (Figure 1).

Urticaria control test, dermatology quality of life index, patient's global assessment of disease severity and physician's global assessment of disease control scores of patients who responded to antihistamines

At the second visit, the mean UCT scores and PhyGA-VAS scores of sg-AH responders (n=40) were increased significantly ($p<0.001$), while DLQI scores and PatGA-VAS decreased ($p<0.001$) (Table 1).

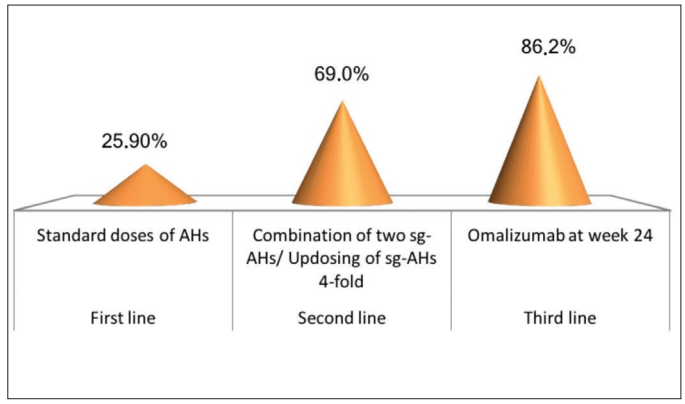

Figure 1. Total response rates of patients with SD to 1st line, 2nd line and 3rd line therapies by using Urticaria control test (UCT) (responders are defined as patients with UCT scores of ≥12)
sg-AHs: Second generation-antihistamines, SD: Standard deviation

Urticaria control test, dermatology quality of life index, patient's global assessment of disease severity, and physician's global assessment of disease control scores of patients on omalizumab

Omalizumab treatment was introduced to 12 patients and these patients were followed for 12 weeks. Four patients were lost to follow up after 12 weeks. When the mean parameters were compared with baseline and week 12, the mean UCT score and PhyGA-VAS were found to be increased significantly (p=0.002, p=0.002), DLQI scores, and PatGA-VAS decreased significantly (p=0.002, p=0.003). At week 24, all these parameters also changed significantly compared to baseline (UCT: p=0.012, DLQI: p=0.012, PhyGA-VAS: p=0.012, PatGA-VAS: p=0.016) (Table 2) (Figure 2).

Discussion

SD is a debilitating condition that impairs QoL significantly and may require further treatment[15,16]. Recommended treatment for chronic inducible urticaria (CIndU) is the same as that for CSU[17-19]. Primary treatment of SD includes the avoidance of any trigger and total symptom control[3,20]. Trigger avoidance is not always easy and most patients require symptomatic treatment[3,21]. Standard dose of a sg-H1-AH is the first line treatment for SD which is the recommended treatment modality by the guidelines both for CIndU and CSU[1,6]. Most of the SD patients respond to sg-H1-AH but significant proportion of the cases are AH resistant[22,23]. Standard doses of cetirizine, acrivastine and terfenadine are reported to be effective while there is only one study of updosing of ebastine (20 mg) reported to be effective and safe as an updosing AH treatment in SD[15,17,24,25].

Physical urticarias (PU) are reported to be less likely to resolve compared to CSU (after 1 year 16.4% versus 47.4%, respectively), and treatment of PUs with the standard dose of AHs are often insufficient, a study reported that patients who gained little or no benefit from the H1 receptor antagonists were more likely to have PU[23,26-29]. Kocatürk et al.[19] showed that CIndU patients responded lower than patients with CSU to standard doses of sg-AHs (20.9% vs 37.9) but no difference observed for the higher doses of sg-AHs. In this study 69% of the SD patients were found to be responders to sg-H1-AHs. Similar to our study 72% of SD patients taking H1-AHs had a marked improvement or were completely free of symptoms[5]. Additionally, we have showed that only 25.9% (n=15) of the patients responding to standard doses. The mean UCT and PhyGA-VAS increased significantly while mean DLQI, PatGA-VAS decreased significantly as response to sg-H1-AHs. In previous reports, 30-50% of chronic urticaria (CU) patients were resistant to AHs and needed further treatment[30,31]. In our study second line therapy increased the response rate but %31 (n=18) patients with SD were refractory to sg-H1-AH and required third line treatments.

In the latest guidelines, the only third line treatment is omalizumab[6,7]. Recommended next step for the patients with severe disease who are resistant to any dose of AHs and omalizumab in combination is cyclosporine[6]. But all these treatments are off-label for patients with SD except for the AHs. Narrowband ultraviolet B phototherapy and psoralen photochemotherapy have been reported as effective in SD patients[1]. Responses to omalizumab treatment were reported to be similar in patients with CIndU and CSU patients in real life experiences[18,19,32]. The effectiveness of omalizumab in patients with SD has been shown in a recent randomized placebo-controlled clinical trial as well as a case report and case series[4,22,23,28,32-34].

In a report of clinical series, delayed pressure urticaria and SD were found to be more responsive to omalizumab treatment and 86% (6/7) of the patients with SD showed complete response while 1 patient showed significant improvement[32]. In other two series one of two patients with SD showed response to omalizumab treatment[28,34]. One case report also showed total response to omalizumab[22]. And in another series, retreatment with omalizumab showed rapid response in 3 patients with SD after first injection[33].

In a randomized, placebo-controlled trial, critical friction thresholds improved significantly at week 10 of treatment in both doses as well as rapid improvement in friction thresholds was observed at week 4. Complete response was achieved in 8 (44%) patients with 150 mg of omalizumab, in 10 (53%) with 300 mg while it was achieved by 2 patients (11%) in the placebo group at week 10. But both doses of omalizumab were found to be effective with no statistical differences[4].

In our study, 9 of 12 patients (75%) responded to omalizumab

Table 1. Mean UCT, DLQI, PatGA-VAS and PhyGA-Vas of patients with SD who responded to sg-H1-AHs

Symptomatic dermographism n=40	1st visit	2nd visit	p
UCT score			
Minimum-maximum (median) Mean ± SD	**3-16 (9)** 9.75±3.26	**12-16 (13)** 13.42±1.47	**<0.001**
DLQI score			
Minimum-maximum (median) Mean ± SD	**0-20 (5)** 6.65±5.45	**0-12 (2)** 3.03±2.87	**<0.001**
PatGA-VAS			
Minimum-maximum (median) Mean ± SD	**0-8 (4)** 4.05±2.32	**0-8 (2)** 2.62±1.89	**<0.001**
PhyGA-VAS			
Minimum-maximum (median) Mean ± SD	**3-10 (6.5)** 6.62±2.05	**5-10 (9)** 8.27±1.24	**<0.001**

UCT: Urticaria control test, DLQI: Dermatology life quality index, PatGA-VAS: Patient's global assessment of disease severity, PhyGA-VAS: Physician's global assessment of disease control, SD: Standard deviation

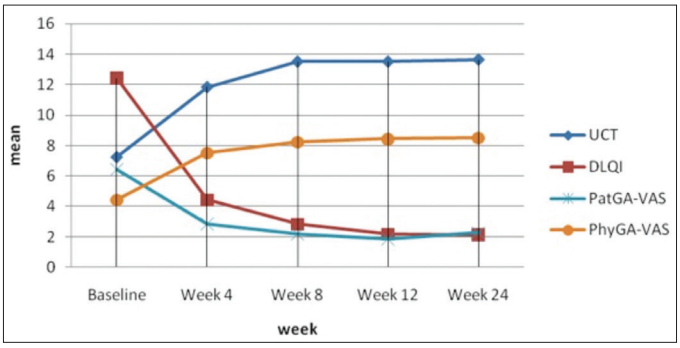

Figure 2. Mean UCT, DLQI, PhyGA-Vas, and PatGA-VAS of SD patients at baseline (week 0), 4th, 8th, 12th and 24th weeks of omalizumab treatment

UCT: Urticaria control test, DLQI: Dermatology life quality index, PhyGA-Vas: Physician's global assessment of disease control, PatGA-VAS: Patient's global assessment of disease severity, SD: Standard deviation

Table 2. Mean UCT, DLQI, PhyGA-Vas, and PatGA-VAS of SD patients and disease control at baseline (week 0) and 4th, 8th, 12th and 24th weeks of omalizumab treatment

SD	UCT score	Disease control		DLQI score	PhyGA-VAS	PatGA-VAS
	Minimum-maximum (median) mean ± SD	UCT <12	UCT ≥12	Minimum-maximum (median) mean ± SD	Minimum-maximum (median) mean ± SD	Minimum-maximum (median) mean ± sd
		n (%)	n (%)			
Baseline (n=12)	2-11 (9) 7.25±3.05	12 (100%)	0	2-27 (9) 12.42±8.69	2-6 (5) 4.42±1.51	3-10 (7) 6.42±2.02
Week 4 (n=12)	8-15 (13) 11.83±2.08	5 (41.7%)	7 (58.3%)	0-18 (2) 4.42±6.08	3-9 (9) 7.50±2.11	1-6 (3) 2.83±1.90
Week 8 (n=12)	10-16 (14) 13.50±2.02	2 (16.7%)	10 (83.3%)	0-14 (1) 2.83±4.47	4-10 (9) 8.25±1.54	0-8 (1) 2.17±2.25
Week 12 (n=12)	10-16 (15) 13.50±2.20	3 (25%)	9 (75%)	0-11 (1) 2.17±3.95	5-10 (9) 8.42±1.31	0-6 (1) 1.83±1.80
Week 24 (n=8)	11-16 (14) 13.63±1.92	1 (12.5%)	7 (87.5%)	0-7 (1) 2.13±2.53	7-9 (9) 8.50±0.76	1-5 (2) 2.25±1.49
Baseline-week 12 (n=12)	**p=0.002**	-		**p=0.002**	**p=0.002**	**p=0.003**
Baseline-week 24 (n=8)	**p=0.012**	-		**p=0.012**	**p=0.012**	**p=0.016**

UCT: Urticaria control test, DLQI: Dermatology life quality index, PatGA-VAS: Patient's global assessment of disease severity, PhyGA-VAS: Physician's global assessment of disease control, SD: Standard deviation

therapy while this rate increased to 87.5% at week 24 (7/8 patients). In our previous report, 6 of 7 SD patients responded to omalizumab treatment at week 24[19]. Reported response rates of omalizumab treatment in real-life studies and many clinical trials in CU is 52-90% while retrospective clinical analysis 83% of CSU cases and 70% of the patients with CIndU showed complete remission[32,35]. Our previous study revealed the response rates as 78.6% in patients with CIndU, 84.6% in patients with CSU[19]. In current study, mean DLQI and PatGA-VAS decreased while mean UCT and PhyGA-VAS increased significantly following omalizumab treatment from baseline to week 12 and 24 which point the importance of continuing treatment up to 24 weeks before deciding omalizumab provided relief or not. Response rates to omalizumab (87.5% at week 24) of patients with SD in this study is found to be similar with the reported responses to CSU patients[36].

Study Limitation

The size of the sample is small, the design of the study is not placebo-controlled and treatment responses could be compared with the results of patients with CSU. Threshold testing and change in critical friction thresholds should be determined in future studies.

Conclusion

Approximately 70% of SD patients responded to sg-AHs and with the introduction of omalizumab into treatment, only a small percentage of patients remained unresponsive to recommended treatments. Using disease activity tools such as UCT and QoL measures provides better assessment of treatment responses and a better patient care.

Ethics

Ethics Committee Approval: This study was approved by İstanbul Okmeydanı Training and Research Hospital Institutional Review Board (approval number: 525, 48670771-514) and was conducted according to the principles of the Declaration of Helsinki.

Informed Consent: All participants provided written informed consent.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: P.K.C., E.K., Concept: P.K.C., E.K., Design: P.K.C., E.K., Data Collection or Processing: P.K.C., E.K., Analysis or Interpretation: P.K.C., Literature Search: P.K.C., E.K., Writing: P.K.C., E.K.

Conflict of Interest: Emek Kocatürk MD, reports advisory board fees from Novartis, and has served as a medical advisor for Bayer. The other authors have no conflict of interest to declare.

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