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EFFECT OF DRUG DESENSITIZATION ON DRUG HYPERSENSITIVITY RELATED QUALITY OF LIFE

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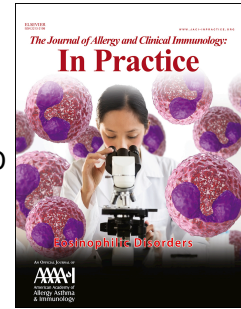
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RELATED QUALITY OF LIFE**

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31 **Conflict of Interest**

32 The authors declare that the research was conducted in the absence of any commercial or
33 financial relationships that could be construed as a potential conflict of interest.

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38 **Clinical Implications:**

39 The health-related quality of life scores of patients with drug hypersensitivity significantly
40 improves after drug desensitization. Drug Hypersensitivity Quality of Life Questionnaire
41 (DrHy-Q) can be used in patients with drug hypersensitivity for evaluating quality of life
42 response to therapeutic interventions.

43

44 **Key words.** Drug allergy, Drug desensitization, Drug hypersensitivity, Drug Hypersensitivity
45 Quality of Life Questionnaire, Quality of life, Responsiveness.

46

Trying to avoid exposure to drugs, anxiety about recurrence of an allergic reaction and concerns about using drugs may adversely affect quality of life (QoL) in patients with drug hypersensitivity (1,2). The only specific tool measuring health-related QoL in patients with drug hypersensitivity was developed by an Italian group in 2011 (DrHy-Q: Drug Hypersensitivity Quality of Life Questionnaire) (3). DrHy-Q is a reliable and valid instrument for evaluating QoL in patients with drug hypersensitivity (3). The Turkish version of the DrHy-Q was found reliable and valid for evaluating QoL in patients with drug hypersensitivity in 2016 (1). Drug desensitization is used to prevent the occurrence of an allergic reaction in sensitized patients, when substitutions with an alternative are not possible or not as effective as the culprit drug (4,5). It is defined as the induction of a temporary tolerance of a compound responsible for a hypersensitivity reaction which is maintained by continuous administration of the medication.

DrHy-Q has been shown to be responsive to the interventions such as diagnostic interventions (skin tests and/or provocation tests), and provocation tests for finding safe alternative drugs or drug desensitization in a limited number of studies (1,6). However, the impact of drug desensitization on responsiveness has not been evaluated specifically. We aimed to evaluate the effect of drug desensitization on disease-specific QoL assessed using DrHy-Q in this prospective, multicenter study, performed in six Allergy-Immunology units in Turkey.

DrHy-Q includes 15 items evaluated on a five-point Likert scale (Table E1). It was designed to be completed by the patient, and higher scores reflect worse QoL (3). The validated Turkish version of the DrHy-Q which did not include major differentiation from the original Italian version other than linguistic adaptation was used in this study (1). The DrHy-Q was performed within one hour before and after desensitization. The inclusion criteria were an age of at least 18 years, to have objective symptoms compatible with drug hypersensitivity, a diagnosis of drug hypersensitivity and to have an indication of drug desensitization with the

culprit drug. All patients gave written informed consent and the Local Ethics Committee at the Ankara University approved the protocol. A total of 111 patients were included in the study.

To detect a moderate effect size (Cohen's $d=0.5$) between the total scores before and after desensitization (95% confidence, 80% power level), at least 35 subjects were required (7). Sample size was calculated with G*Power v.3.1 package program (8). Wilcoxon signed-rank test was used to evaluate the difference between the scores of the DrHy-Q before and after desensitization. Percentage change values before and after desensitization DrHy-Q scores were calculated with the formula $[(\text{before DrHy-Q} - \text{after DrHy-Q}) / \text{before DrHy-Q}] * 100$. The difference between the independent groups in terms of percentage change in scale scores was evaluated by Mann-Whitney U test or Kruskal-Wallis test. Statistical analyses were performed using Rv3.6.1. $P < 0.05$ was considered statistically significant.

Demographic and clinical characteristics of the patients are shown in Table1. The most common implicated drugs to hypersensitivity reactions were chemotherapeutic drugs (71/111 patients, 64.0%) and biological drugs (22/111 patients, 19.8%). The most frequently desensitized drugs were carboplatin (n:27), rituximab (n:14), oxaliplatin (n:13), docetaxel (n:10), paclitaxel (n:9), and acetyl salicylic acid (n:7). Breakthrough reactions during desensitizations were observed in 19.9% (n:22) of the patients. They were often grade-1 (10%, n:11), grade-2 (9%, n:10) and one patient had grade-3 reaction.

The baseline DrHy-Q scores before desensitization were significantly higher than the post-desensitization DrHy-Q scores (Wilcoxon Signed-Ranks Test $p < 0.001$) (Table2, FigureE1). The effect size was 0.53, which can be considered as a medium magnitude of effect. Percentage change in DrHy-Q scale was median 7.7% (min;max -50;68%) (Table2). The percentage changes in the DrHy-Q scores did not differ significantly according to gender, education level, the culprit drugs, indications of the culprit drugs, skin test and/or provocation

test results with the culprit drug, severity of the drug hypersensitivity reaction, presence of a breakthrough reaction during desensitization, the route and method of desensitization (oral/subcutaneous vs. intravenous and rapid drug desensitization (RDD) vs. non-rapid drug desensitization (non-RDD)) and presence of a psychiatric comorbidity (Table2).

This study provides information regarding the disease specific QoL, in a population consisting of 111 patients with drug hypersensitivity mainly due to chemotherapeutics and biologicals and shows that drug desensitization improves disease specific QoL in this population. To our knowledge, disease specific QoL in patients with hypersensitivity to chemotherapeutics and biologicals is evaluated for the first time in this study. The median baseline DrHy-Q score of 41 (min;max, 15;73) observed in this study was higher than that reported in previous studies (1,3,6,9). This difference could be explained by the different characteristics of the study groups. While the majority of our patients were hypersensitive to chemotherapeutics and biologicals, previous studies from Turkey (1), the Netherlands (9) consisted from patients with drug hypersensitivity mainly due to antibiotics and non-steroidal anti-inflammatory drugs. As we used an indication of drug desensitization as an inclusion criterion, our population had considerably more comorbid diseases (91%) compared to the previous studies (1,9). The fact that patients with major comorbid diseases realized that they could receive the planned therapies with desensitization may positively affect the DrHy-Q. On the other hand, in these major chronic diseases like malignant diseases, alternative drugs may be more restricted. Therefore, fear and anxiety that the chronic disease will not be adequately treated due to the inability to use first-line drugs may have additional negative impacts on quality of life of our patients.

Responsiveness of DrHy-Q to interventions such as diagnostics tests, finding safe alternative drugs or drug desensitization was evaluated previously in two studies (1,6). In the first study, we evaluated responsiveness in 97 patients among 717 subjects and showed that DrHy-Q was

able to detect improvement of health-related QoL after interventions as finding safe alternative drug or drug desensitization (1). However, that study had not been systematically designed to evaluate which intervention specifically influences responsiveness. The second previous study, included 360 patients and found the diagnostic allergy study caused an improvement in QoL after obtaining a conclusive diagnosis(6).

Our results show for the first time that the health-related QoL of patients with drug hypersensitivity significantly improves after drug desensitization. A median 8% decrease was observed in the DrHy-Q score after drug desensitization. This improvement does not seem to be affected by the implicated drugs, indications of the implicated drugs, severity of the initial drug hypersensitivity reaction and to develop a breakthrough reaction during desensitization. We propose that DrHy-Q can be used in patients with drug hypersensitivity for evaluating quality of life response to therapeutic interventions.

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Table 1: Demographic and clinical characteristics of the patients (n=111)

Age (years), median (min;max)	53 (18;79)
Female / male, n (%)	91 (82.0) / 20 (18.0)
Education, n (%)	
Primary school	35 (31.6)
Secondary school	16 (14.4)
High school	32 (28.8)
University	28 (25.2)
Occupation, n (%)	
Housewife	71 (64.0)
Worker	11 (10.0)
Officer	7 (6.2)
Independent business owner	5 (4.5)
Retired	12 (10.8)
Student	5 (4.5)
Indication of the drug, n (%)	
Malignant disease	88 (79.3)
Rheumatological / autoimmune disease	13 (11.7)
Nasal polyps	6 (5.4)
Others	4 (3.6)
Drugs, n (%)	
Chemotherapeutic	71 (64.0)
Biological	22 (19.8)
NSAID	7 (6.3)
Antibiotics	2 (1.8)
Hormone therapy	2 (1.8)
Others	7 (6.3)
Diagnostic methods, n (%)	
Reliable history only	102 (91.9)
Reliable history and skin tests	6 (5.4)
Reliable history and provocation tests	3 (2.7)
Initial DHR grade, n (%)	
I	10 (9.0)
II	65 (58.6)
III	36 (32.4)
Type of symptoms of the initial DHR, n (%)	
Urticaria and/or AE	16 (17.1)
Respiratory reaction	22 (19.8)
Anaphylaxis	42 (37.8)
Delayed-type cutaneous reaction	4 (3.6)
Urticaria and/or AE and URS	27 (21.7)
Breakthrough reaction during desensitization, n (%)	
No	89 (80.1)
Yes	22 (19.9)

Concomitant allergic diseases (yes/no), n (%)	23/88 (20.7 / 79.3)
Allergic rhinitis	6 (5.4)
Asthma	7 (6.3)
Allergic rhinitis and asthma	7 (6.3)
Venom hypersensitivity	2 (1.8)
Other	1 (0.9)
Comorbid diseases, n (%)	
Malignant diseases	88 (79.3)
Cardiovascular diseases	21 (18.9)
Rheumatological / autoimmune diseases	13 (11.7)
Endocrine diseases	10 (9.0)
Nasal polyps	6 (5.4)
Gastrointestinal diseases	6 (5.4)
Respiratory diseases	2 (1.8)
Other	5 (3.6)
Psychiatric comorbidity (yes/no), n (%)	10 / 101 (9.0/ 91.0)
Depression	8 (7.2)
Anxiety disorder	2 (1.8)

NSAID: Non-steroidal anti-inflammatory drug; DHR: Drug hypersensitivity reaction; AE: Angioedema; URS: mild upper respiratory symptoms; DPT: Drug provocation test; Np: not performed; ASA: Acetylsalicylic acid.

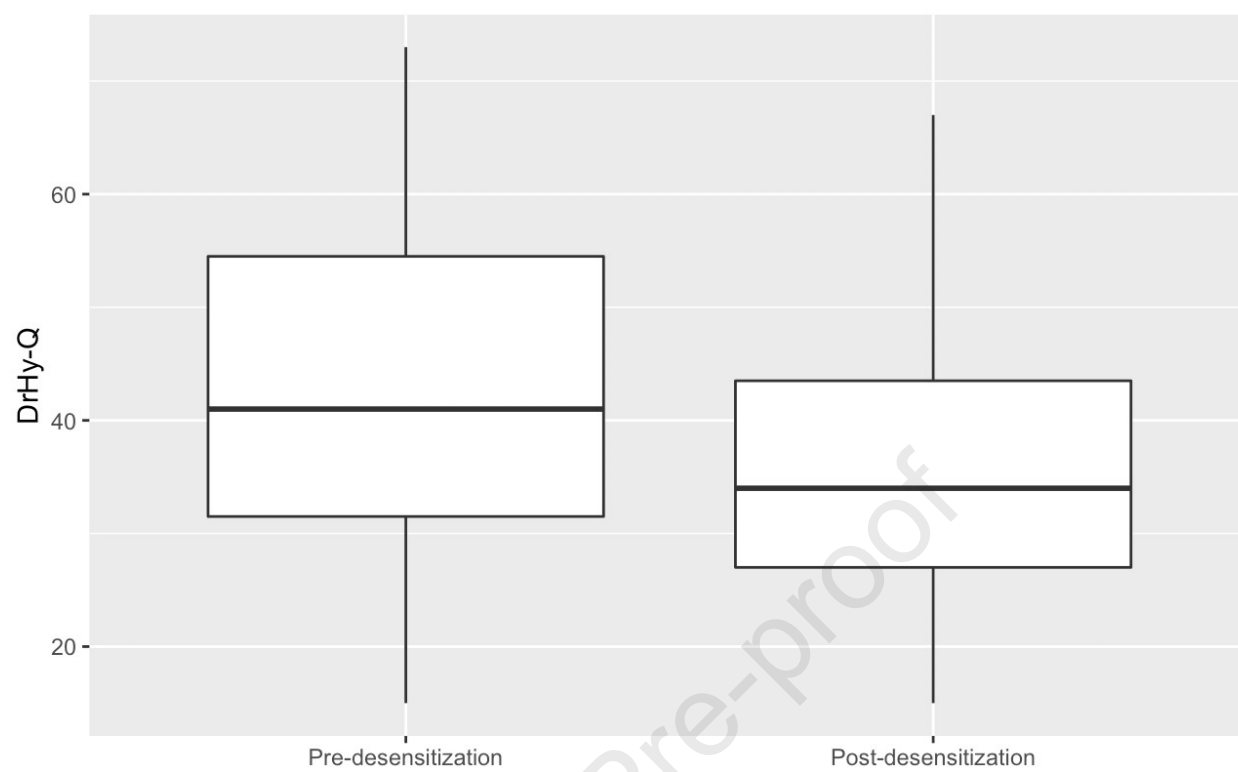
Table 2: DrHy-Q scale scores and percentage changes in DrHy-Q scale scores.

	DrHy-Q scale scores, median (min;max)		Percentage change in DrHy-Q (%)*, median (min;max)	P value
	Pre-desensitization	Post-desensitization		
DrHy-Q scale	41.0 (15.0;73.0)	34.0 (14.0;67.0)	7.7 (-50.0;68.0)	< 0.001 ^a
Gender				
Female	42.0 (15.0;73.0)	35.0 (15.0;66.0)	10.0 (-50.0;68.5)	0.390 ^b
Male	34.5 (16.0;65.0)	29.5 (15.0;67.0)	1.2 (-11.1;51.6)	
Education				
Primary school	52.0 (19.0;73.0)	38.5 (15.0;61.0)	8.8 (-24.4;68.5)	0.658 ^c
Secondary school	48.0 (20.0;67.0)	34.5 (23.0;58.0)	16.7 (-25.7;54.9)	
High school	29.5 (15.0;68.0)	31.0 (15.0;67.0)	6.1 (-4.9;63.2)	
University	33.0 (16.0;64.0)	29.0 (14.0;66.0)	4.7 (-50.0;86.1)	
Drugs				
Chemotherapeutic	42.0 (15.0;73.0)	35.0 (15.0;67.0)	8.0 (-43.9;68.5)	0.362 ^c
Biologic	38.0 (20.0;61.0)	32.0 (15.0;66.0)	5.9 (-24.3;50.8)	
NSAID	55.0 (23.0;68.0)	30.0 (25.0;66.0)	18.9 (-17.3;63.2)	
Others	36.0 (16.0;64.0)	40.0 (15.0;62.0)	4.6 (-50.0;50.0)	
Skin test and provocation				
Negative	58.0 (22.0;67.0)	41.0 (20.0;67.0)	11.0 (-3.1;55.0)	0.558 ^b
Positive	51.0 (22.0;68.0)	42.0 (20.0;67.0)	6.7 (-50.0;68.5)	
Type of symptoms of the DHR				
Urticaria and/or AE	38.0 (18.0;68.0)	34.0 (15.0;66.0)	10.7 (-25.7;50.0)	0.147 ^c
Respiratory reaction	36.0 (19.0;68.0)	28.0 (21.0;66.0)	0 (-21.7;63.2)	
Anaphylaxis	42.0 (16.0;67.0)	35.0 (15.0;61.0)	10.5 (-50.0;51.8)	
Urticaria + URS	49.0 (15.0;73.0)	38.0 (15.0;67.0)	11.0 (-22.0;69.0)	
Initial DHR grade				
I	36.0 (19.0;68.0)	28.0 (16.0;66.0)	12.1 (-21.7;50.0)	0.890 ^c
II	41.0 (15.0;73.0)	34.0 (15.0;67.0)	6.0 (-50.0;68.5)	
III	43.0 (16.0;67.0)	35.0 (15.0;61.0)	11.0 (-43.9;58.7)	
Indication of the culprit drug				
Malignant disease	39.0 (15.0;73.0)	34.0 (15.0;67.0)	6.5 (-43.9;68.5)	0.320 ^c
Rheumatological / autoimmune disease	47.0 (33.0;64.0)	38.0 (21.0;66.0)	13.8 (-13.8;50.8)	
Others	55.0 (23.0;68.0)	34.0 (16.0;66.0)	18.9 (-50.0;63.2)	
Breakthrough reaction during desensitization				
No	39.0 (15.0;73.0)	34.0 (15.0;67.0)	6.2 (-50.0;68.4)	0.685 ^b
Yes	42.5 (18.0;68.0)	38.5 (15.0;66.0)	17.4 (-25.7;50.0)	
Psychiatric comorbidity				
No	41.0 (15.0;68.0)	35.0 (15.0;66.0)	6.6 (-50.0;63.2)	0.150 ^b
Yes	43.5 (32.0;73.0)	32.5 (16.0;67.0)	12.5 (-5.0;68.5)	
Method				
Non-RDD	44.0 (16.0;68.0)	38.5 (15.0;66.0)	6.2 (-50.0;63.2)	0.512 ^b
RDD	40 (15.0;73.0)	34.0 (15.0;67.0)	8 (44.0;68.5)	

P values are based on a: Wilcoxon signed-rank test, b: Mann Whitney U test, c: Kruskal Wallis test. * Percentage change values before and after DrHy-Q scores were calculated with the formula $[(\text{before DrHy-Q} - \text{after DrHy-Q}) / \text{before DrHy-Q}] * 100$.

NSAID: Non-steroidal anti-inflammatory drug; DHR: Drug hypersensitivity reaction; AE: Angioedema; URS: mild upper respiratory symptoms; RDD: Rapid drug desensitization.

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Online repository Table:

Table E1: Items of Drug Hypersensitivity Quality of Life Questionnaire (1,3).

Items
Since I am unable to take drugs every illness limits me more than other people. I am afraid of being administered a drug during an emergency to which I am allergic. I feel frightened due to my problem of allergy reaction. The problem of adverse reaction to drugs affects my life. I would like the allergist's opinion before taking drugs prescribed by other specialists. Even a little discomfort for me is a problem. I feel different from others. I feel anxious due to my problem of allergy reaction. For each disease I would be confident that there is a drug that I can safely take. I am afraid I could not deal with the pain. I feel anguished due to my problem of allergy reaction. I worry every time I take a drug different from ones that cause my allergic reactions. I give up leisure activities (sport, vacations, trips) because of my problem. I'm in a bad mood due to my problem of allergy reaction. The idea of taking a medicine makes me feel anxious.

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Figure E1: Pre-desensitization and post-desensitization DrHy-Q scale scores (The central box represents the values from the lower to the upper quartile (25th and 75th percentile), the line within the box indicates the median and the whiskers show the minimum and maximum).