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**Healthcare Services Utilization and Drug use in Patients with Chronic Urticaria**

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***Abbreviations and acronyms***

|                        |     |
|------------------------|-----|
| Chronic urticaria      | CU  |
| Clalit Health Services | CHS |
| Emergency room         | ER  |
| Intensive care unit    | ICU |
| Over the counter       | OTC |

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**TO THE EDITOR**

Chronic urticaria (CU) is defined as continuous urticaria occurring in a period of 6 weeks or more while off treatment (Zuberbier, 2012). Second-generation antihistamines with up-dosing up to fourfold constitute the first- and second-line treatments for CU, and are the mainstay of pharmacologic management for most patients. About 40-70% of patients attending tertiary care clinics will become symptom-free at appropriate doses of antihistamines treatment. Antihistamine therapy failure is considered only after the patient does not respond to augmented dosage (Zuberbier et al, 2014). Third-line therapies, is used as add-on therapy and include omalizumab, cyclosporine, and the leukotriene receptor antagonist, montelukast. Many other treatments have been used in patients with refractory CU such as sulfasalazine, colchicine, methotrexate, mycophenolate mofetil, azathioprine, and cyclophosphamide (Di Lorenzo et al, 2008, Pho et al, 2011, Orden et al, 2014, Grattan et al, 1992, Jiang et al, 2008, Mitzel-Kaoukhov et al, 2010, Grattan et al, 2000, Perez et al, 2010). Nonetheless, the level of evidence supporting use of the modalities beyond third-line treatments is rather weak and based on anecdotal reports or small case series. Notably, systemic corticosteroids may eliminate urticarial lesions in the short-term; however, their long-term use (more than 10 days) is undesirable due to cumulative severe adverse effects (Makris et al, 2013, Zuberbier et al, 2014).

The aim of our study was to investigate utilization of health-care services and drug use among patients with CU using a large community-based database from Clalit Health Services.

Our study was designed as a cross-sectional study of CU patients and age- and gender-matched controls, based on Clalit Health Services (CHS) database - a large public healthcare provider organization in Israel.

We used a conservative definition for CU as follows: 4 couples of urticaria diagnoses, recorded within a period of 6 weeks, registered by physicians in community services, out-patient clinics, or during hospitalization, from January 2002 to December 2012. The control group consisted of randomly selected age- and gender-matched patients without CU, extracted from the general population of CHS enrollees. Patients with one or more diagnoses of urticaria were excluded from the control group.

Health-care services utilization during 2013 was extracted for both cases and controls. Drug use data was based on pharmacy claims during 2013. Since approximately 50% of CU patients experience spontaneous resolution within 6-12 months from symptoms onset, patients with high use of CU-related medications during 2013 were considered patients with persistent disease. In order to assess the number of patients with chronic steroid treatment, we evaluated the lag period between two consecutive systemic corticosteroid prescriptions among patients treated with more than one prescription. This subgroup of patients was sub-divided according to the lag period between two consecutive prescriptions: 30, 45, and 60 days. Patients with lag period of 60 days between consecutive prescriptions were considered as chronic steroid users.

Statistical analysis was performed using analysis of variance (ANOVA) or T-tests, Pearson's chi-square or Fisher's exact test, as appropriate, using the SPSS package, version 20 (SPSS Inc., Chicago, IL, USA). All statistical tests performed were 2-sided;  $p$ -value  $< 0.05$  was considered statistically significant.

The study included 11,271 patients with CU and 67,216 controls, representing a prevalence of 0.27% among CHS enrollees. We observed female gender predominance of 66%, with an average age of 47.4 ( $\pm 22$ ) years, in correlation with

previous reports. 1,329 (11.8%) patients with CU were younger than 20 years at diagnosis. CU patients had high proportions of atopic diathesis (19.9%, 10.8%, 9.8% in CU cases vs 10.1%, 6.5% and 3.7% in controls, of allergic rhinitis, asthma and atopic dermatitis, respectively,  $p < 0.001$ ).

We observed an increased health-care services utilization and drug use among CU patients. Health care services utilization during 2013 is presented in Table 1. The comparative analysis between the two groups revealed a consistent higher health-care services usage among the CU patients. Drug use during 2013 among cases and control is presented in Table 2. Forty five percent of patients had persistent disease prompting use of CU-related medications during 2013. Forty-two percent of the CU patients were treated with antihistamines, 24% with systemic corticosteroids and less than 2% of the patients were treated with third-line therapies. Systemic corticosteroids accounted for the majority of the treatments prescribed for CU other than antihistamines, with a prolonged steroids use observed in 10.5% of the patients, while other therapies (i.e., montelukast and cyclosporine) were used by less than 5% of CU patients. Worth noting that patient management variations may exist between-country, therefore this observation may not be fully generalizable to other settings.

Prolonged use of systemic corticosteroids may cause severe adverse effects, which may not be evident in short-term management. Switching from second-line therapies to third-line treatments and not to systemic corticosteroids may prove to be more economic, decreasing health-care services utilization.

In conclusion, our observations suggests that the use of third-line therapies should be augmented at the outset of antihistamine treatment failure among patients with CU in the community setting. The use of safer and more efficient drugs after antihistamine treatment failure is warranted in patients with CU.

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**Conflict of Interest:**

Prof. Arnon Cohen: Relationships relevant to this manuscript: Prof. Arnon Cohen received research grants from Novartis. Other relationships: In the last 3 years, Prof. Arnon Cohen served as a consultant, advisor or speaker to Abbvie, Dexcel pharma, Janssen, Novartis, Perrigo, Pfizer, and Rafa. All other authors have no conflict of interest to disclose.

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**Author Contributions:**

Dr. Guy Shalom, Dr. Doron Comaneshter, and Prof. Arnon D. Cohen had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

***Study concept and design:*** Dr. Guy Shalom, Prof. Arnon D. Cohen, and Prof. Nancy Agmon-Levin.

***Acquisition, analysis, and interpretation of data:*** Dr. Guy Shalom, Prof. Arnon D. Cohen, Prof. Nancy Agmon-Levin, and Dr. Doron Comaneshter.

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***Critical revision of the manuscript for important intellectual content:*** Drs Shalom and Dennis Linder, Prof. A.D. Cohen, Prof Nancy Agmon-Levin, Prof. Bitterman, Drs Alexandra Nathan.

***Statistical analysis:*** Dr. Doron Comaneshter, Prof. A.D. Cohen, and Dr. Shalom.

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**Study supervision:** Prof. Arnon D. Cohen and Prof. Nancy Agmon-Levin.

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Table 1. Comparative analysis of health care services utilization among patients with CU and controls during 2013.

| Health-care service                                                                               | Chronic urticaria | Control group | <i>p</i> -value |
|---------------------------------------------------------------------------------------------------|-------------------|---------------|-----------------|
|                                                                                                   | n=11,271          | n=67,216      |                 |
| Community services                                                                                |                   |               |                 |
| General practitioner community clinic visits; mean (SD)                                           | 12.2 (41.6)       | 8.6 (9.4)     | <0.001          |
| Dermatologist community clinic visits; mean (SD)                                                  | 0.68 (2.2)        | 0.32 (0.9)    | <0.001          |
| Pediatric clinic visits; mean (SD)                                                                | 1.44 (9.7)        | 0.8 (2.9)     | <0.001          |
| Allergy community clinic visits; mean (SD)                                                        | 0.2 (0.9)         | 0.12 (0.2)    | <0.001          |
| In- and out-patient services                                                                      |                   |               |                 |
| Internal emergency room visits                                                                    | 2,782 (24.7)      | 12,255 (18.2) | <0.001          |
| Proportion of patients who were hospitalized in internal medicine departments during 2013         | 1,546 (13.7)      | 3,611 (5.4)   | <0.001          |
| Proportion of patients who were hospitalized in internal medicine departments >7 days during 2013 | 357 (3.2)         | 1,567 (2.3)   | <0.001          |
| Proportion of patients who were hospitalized in the intensive care units during 2013              | 99 (0.9)          | 464 (0.7)     | 0.028           |
| Dermatology department hospitalizations                                                           | 125 (1.1)         | 87 (0.1)      | <0.001          |

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Table 2. Comparative analysis of drug use during 2013 among cases and control.

|                                              | Chronic urticaria<br>n=11,271<br>n (%) | Control group<br>n=67,216<br>n (%) | OR   | 95% CI    | p-Value |
|----------------------------------------------|----------------------------------------|------------------------------------|------|-----------|---------|
| <b>Systemic antihistamines prescriptions</b> | 4,740 (42.1)                           | 8,246 (12.3)                       | 5.2  | 4.9-5.4   | <0.001  |
| <b>1<sup>st</sup> generation</b>             |                                        |                                    |      |           |         |
| Chlorphenamine                               | 789 (7)                                | 714 (1.1)                          | 7    | 6.3-7.8   | <0.001  |
| Doxylamine                                   | 24 (0.2)                               | 112 (0.2)                          | 1.3  | 0.8-1.9   | NS      |
| Hydroxyzine                                  | 207 (1.8)                              | 69 (0.1)                           | 18.2 | 13.9-23.9 | <0.001  |
| Promethazine                                 | 438 (3.9)                              | 769 (1.1)                          | 3.5  | 3.1-3.9   | <0.001  |
| <b>Total</b>                                 | 1,255 (11.1)                           | 1,600 (2.4)                        | 5.1  | 4.8-5.6   | <0.001' |
| <b>2<sup>nd</sup> generation</b>             |                                        |                                    |      |           |         |
| Mizolastine                                  | 393 (3.5)                              | 97 (0.1)                           | 25   | 20-31.3   | <0.001  |
| Cetirizine                                   | 977 (8.7)                              | 1,034 (1.5)                        | 6.9  | 5.6-6.7   | <0.001  |
| Dimethindene                                 | 208 (1.8)                              | 386 (0.6)                          | 3.3  | 2.8-3.9   | <0.001  |
| Ketotifen                                    | 195 (1.7)                              | 88 (0.1)                           | 13.4 | 10.4-17.3 | <0.001  |
| Loratadine                                   | 1,010 (9)                              | 2,401 (3.6)                        | 2.6  | 2.5-2.9   | <0.001  |
| <b>Total</b>                                 | 2,288 (20.3)                           | 3,791 (5.6)                        | 4.3  | 4-4.5     | <0.001  |
| <b>Newer 2<sup>nd</sup> generation</b>       |                                        |                                    |      |           |         |
| Desloratidine                                | 1,252 (11.1)                           | 1,286 (1.9)                        | 6.4  | 5.9-6.9   | <0.001  |
| Fexofenadine                                 | 2,753 (24.4)                           | 3,167 (4.7)                        | 6.5  | 6.2-6.9   | <0.001  |
| <b>Total</b>                                 | 3,410 (30.3)                           | 4,200 (6.2)                        | 6.5  | 6.2-6.9   | <0.001  |
| <b>Systemic steroid prescriptions</b>        | 2,671 (23.7)                           | 5,863 (8.7)                        | 3.25 | 3.1-3.4   | <0.001  |
| <b>Montelukast</b>                           | 150 (1.3)                              | 238 (0.4)                          | 1.4  | 1.3-1.5   | <0.001  |
| <b>Cyclosporine A</b>                        | 44 (0.4)                               | 24 (0.04)                          | 2.43 | 1.8-3.4   | <0.001  |
| <b>Sulfasalazine</b>                         | 19 (0.2)                               | 79 (0.1)                           | 1.1  | 0.9-1.17  | NS      |
| <b>Colchicine</b>                            | 98 (0.9)                               | 426 (0.6)                          | 0.77 | 0.6-0.9   | <0.001  |
| <b>Methotrexate</b>                          | 69 (0.6)                               | 272 (0.4)                          | 1.07 | 1.02-1.1  | <0.001  |
| <b>Mycophenolate mofetil</b>                 | 5 (0)                                  | 53 (0.1)                           | 0.94 | 0.9-1.01  | NS      |
| <b>Azathioprine</b>                          | 31 (0.3)                               | 91 (0.1)                           | 0.56 | 0.4-0.6   | <0.001  |
| <b>Cyclophosphamide</b>                      | 3 (0.03)                               | 6 (0)                              | 0.43 | 0.2-1.1   | NS      |