Two-year efficacy, safety, and drug survival of dupilumab for atopic dermatitis: A real-world Canadian multicenter retrospective study

To the Editor: Limited studies are available on the long-term efficacy and safety of dupilumab for moderate-to-severe atopic dermatitis (AD) beyond the 52-week follow-up. A recent publication by our group showed favorable efficacy outcomes with no new safety signals in patients with AD over 52-weeks of dupilumab treatment.1 An observational prospective cohort study of the TREAT NL (TREATment of ATopic eczema, the Netherlands) registry showed consistent safety and efficacy outcomes up to week 84.2 Herein, we aimed to assess the 2-year drug survival of dupilumab in real-world patients with AD.

Following research ethics board approval, we conducted a multicenter retrospective cohort study of all consecutive adult patients (aged ≥18 years) receiving treatment with dupilumab at 3 tertiary academic dermatology clinics in Toronto. Cases

Table I. Reported adverse events and dupilumab discontinuation based on follow-up time

| Variable                                           | Follow-up periods |       |       |       |
|----------------------------------------------------|-------------------|-------|-------|-------|
|                                                    | 0-16 weeks (N = 145) | 16-52 weeks (N = 143) | 52-104 weeks (N = 139) |
| One or more adverse event, n (%)                   | 64 (44)           | 48 (34) | 31 (22) |
| Reported adverse events, n (%)                     |                   |       |       |       |
| Ocular surface disease                              | 45 (31)           | 36 (25) | 18 (13) |
| Infections                                          | 8 (6)             | 3 (2)  | 4 (3)  |
| Oral herpes                                         | 6 (4)             | 1 (1)  | 2 (1)  |
| Cellulitis                                          | 2 (1)             | 1 (1)  | 1 (1)  |
| Cystitis                                            | 1 (1)             | 1 (1)  | 0      |
| Flu-like symptoms                                   | 1 (1)             | 2 (1)  | 0      |
| Upper respiratory tract infection                   | 0                 | 0      | 1 (1)  |
| Skin disorders                                      |                   |       |       |       |
| Injection site reaction                             | 6 (4)             | 2 (1)  | 2 (1)  |
| Head and neck eczema flare or redness               | 2 (1)             | 4 (3)  | 7 (5)  |
| Urticaria                                           | 1 (1)             | 2 (1)  | 2 (1)  |
| Asthma flare                                        | 1 (1)             | 0      | 0      |
| Musculoskeletal                                    |                   |       |       |       |
| Fatigue                                             | 1 (1)             | 0      | 0      |
| Arthralgia                                          | 2 (1)             | 3 (2)  | 0      |
| Headache                                            | 0                 | 0      | 0      |
| Gastrointestinal symptoms                           | 4 (3)             | 2 (1)  | 0      |
| Generalized nonspecific symptoms*                  | 4 (3)             | 2 (1)  | 0      |
| Dupilumab discontinuation, n (%)†                   | 5 (3)             | 20 (14) | 9 (6)  |
| Secondary to adverse event                          | 4 (3)             | 6 (4)  | 4 (3)  |
| Due to lack of efficacy                             | 1 (1)             | 12 (8) | 1 (1)  |
| Non—drug-related reason†                            | 0                 | 2 (1)  | 4 (3)  |

n, Number of subjects meeting criteria.
*Non-specific symptoms include episodes of dizziness, lightheadedness, blurred vision, and/or sweating.
†Patients who discontinued dupilumab due to an adverse event or lack of efficacy were carried forward and included as Investigator Global Assessment nonresponders for each timepoint. Discontinuation due to non—drug-related reasons was excluded from Investigator Global Assessment analysis.
‡Non—drug-related reasons include pregnancy, travel, and loss of insurance drug coverage.

© 2021 by the American Academy of Dermatology, Inc. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
were included if they had moderate-to-severe AD (Investigator Global Assessment [IGA] 3 or 4) at baseline and seen 104 weeks after dupilumab initiation while on therapy. Drug survival was analyzed using unadjusted Kaplan-Meier survival analysis to estimate the risk of and time to discontinuation. Patients were censored if their reason to stop dupilumab treatment was unrelated to efficacy or safety (eg, loss of insurance coverage).

We included 145 patients. The mean (±SD) age was 44.5 ± 14.8 years, and 74 patients (51%) were female. Comorbid conditions included asthma (n = 97; 48.3%), allergic rhinitis (n = 38; 26.2%), and urticaria (n = 15; 10.3%). Patients had failed a median of 2 (range, 0-6) systemic therapies prior to dupilumab.

In total, 85 of 145 patients (59%), 83 of 143 (58%), and 94 of 139 (68%) achieved IGA 0 or 1 (clear or almost clear) at 16, 52, and 104 weeks, respectively. Of the 83 patients with IGA 0/1 at 52 weeks, 74 (89%) maintained IGA 0/1 at 104 weeks. Of the 60 patients with IGA >1 at 52 weeks, 20 (33%) achieved IGA 0/1 at 104 weeks.

In the entire cohort, 89 of 145 patients (61%) reported 1 or more adverse events (AEs) at any point throughout the study period (Table I). New or persistent AEs were reported by 64 of 145 patients (44%), 48 of 143 (34%), and 31 of 139 (22%) between 0 and 16, 16 and 52, and 52 and 104 weeks, respectively. Ocular surface disease was the most commonly reported AE between 52 and 104 weeks (18 of 139 patients; 13%). Drug survival of dupilumab was 97%, 83%, and 80% after 16, 52, and 104 weeks, respectively (Fig 1). Discontinuation of dupilumab treatment was most common between 16 and 52 weeks (20 of 143 patients; 14%) compared with that between 52 and 104 (9 of 139 patients; 6%) and 0 and 16 weeks (5 of 145 patients; 3%) (Table I).

The percentage of patients achieving IGA 0/1 at 104 weeks (68%) is comparable to rates seen in open-label extension studies of phase 3 randomized controlled trials at weeks 76 (57.8%) and 100 (58.1%).3,4 The majority of patients with IGA 0/1 at 52 weeks maintained IGA 0/1 at 104 weeks (89%), and delayed response beyond 52 weeks was less common (33%). In further support of favorable long-term outcomes, all patients on a concomitant systemic therapy (cyclosporine, methotrexate, mycophenolic acid, or prednisone) for at least 12 weeks prior to initiating dupilumab treatment (n = 18; 12%) were able to stop that treatment before 104 weeks. Importantly, drug survival remained high (80%) at
104 weeks of treatment, with the majority of discontinuations occurring between 16 and 52 weeks due to lack of efficacy or AE. No new safety signals were identified beyond 52 weeks, with fewer patients reporting AEs compared with earlier in the treatment period. Limitations of this study include the lack of control arm and reliance on patient charts to assess outcomes.

Overall, these results support the long-term use of dupilumab to achieve sustained control of moderate-to-severe AD in real-world clinical practice.

Jorge R. Georgakopoulos, MD,a Tina Felfeli, MD,b,c Aaron M. Drucker, MD, ScM, FRCPCa,d,e Christine E. Jo, BSc,e Vincent Piguet, MD, PhD, FRCPCa,d and Jensen Yeung, MD, FRCPCa,d,f,g

From the Division of Dermatology, Department of Medicine,a Department of Ophthalmology and Vision Sciences,b and Institute of Health Policy, Management and Evaluation, Dalla Lana School of Public Health, University of Toronto, Ontario, Canada; Women’s College Hospital, Toronto, Ontario, Canada; Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada; Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada; and Probity Medical Research Inc, Waterloo, Ontario, Canada.

Funding sources: None.

IRB approval status: Reviewed and approved by the research ethics board at Sunnybrook Health Sciences Centre (205-2018) and Women’s College Hospital (2018-0079-E).

Correspondence to: Jensen Yeung, MD, FRCP, Department of Dermatology, Women’s College Hospital, 76 Grenville St, Fifth Floor, Toronto, Ontario M5S 1B2, Canada

E-mail: jensen.yeung@utoronto.ca

Conflicts of interest

Dr Drucker has received compensation from the British Journal of Dermatology (reviewer and section editor), American Academy of Dermatology (guidelines writer), and National Eczema Association (grant reviewer). He has been a paid consultant for the Canadian Agency for Drugs and Technology in Health. Dr Piguet has received honoraria or fees for consulting and/or speaking for AbbVie, Almirall, Celgene, Janssen, Novartis, and Pfizer and has received departmental support for Cardiff University from AbbVie, Almirall, Alliance, Beiersdorf UK Ltd, Biotest, Celgene, Dermal, Eli Lilly, Galderma, Genus Pharma, GlobeMicro, Janssen-Celag, LaRoche-Posay, L’Oreal, LEO Pharma, Meda, MSD, Novartis, Pfizer, Sinclair Pharma, Spirit, Stiefel, Samauned, Thornton Ross, TyPham, and UCB and for the University of Toronto from Sanofi. Dr Yeung has been a speaker, consultant, and investigator for AbbVie, Allergan, Amgen, Arcutis, Astellas, Bausch Health, Boehringer Ingelheim, Bristol Meyers Squibb, Celgene, Centocor, Coherus, Dermavant, Dermina, Forward, Galderma, GlaxoSmithKline, Incyte, Janssen, Kyowa, Leo Pharma, Lilly, Medimmune, Merck, Novartis, Pfizer, Regeneron, Roche, Sandoz, Sanofi Genzyme, Sun Pharma, Takeda, UCB, and Xenon. Drs Georgakopoulos and Felfeli and author Jo have no conflicts of interest to declare.

REFERENCES

1. Jo CE, Georgakopoulos JR, Ladda M, et al. Evaluation of long-term efficacy, safety, and reasons for discontinuation of dupilumab for moderate to severe atopic dermatitis in clinical practice: a retrospective cohort study. J Am Acad Dermatol. 2020;82(6):1530-1532.

2. Bosma AL, de Wijs LEM, Hof MH, et al. Long-term effectiveness and safety of treatment with dupilumab in patients with atopic dermatitis: results of the TREAT NL (TREATment of ATopic eczema, the Netherlands) registry. J Am Acad Dermatol. 2020;83(5):1375-1384.

3. Deleuran M, Thaci D, Beck LA, et al. Dupilumab shows long-term safety and efficacy in patients with moderate to severe atopic dermatitis enrolled in a phase 3 open-label extension study. J Am Acad Dermatol. 2020;82(2):377-388.

4. Beck LA, Thaci D, Deleuran M, et al. Dupilumab provides favorable safety and sustained efficacy for up to 3 years in an open-label study of adults with moderate-to-severe atopic dermatitis. Am J Clin Dermatol. 2020;21(4):567-577.

https://doi.org/10.1016/j.jdin.2021.06.001