Dupilumab-Associated Conjunctivitis in Patients With Atopic Dermatitis: A Multicenter Real-Life Experience

Nettis E1, Bonzano L2, Patella V3, Detoraki A4, Trerotoli P5, Lombardo C6, on behalf of the Italian DADReL study group#

1Allergist and Dermatologist Department of Emergency and Organ Transplantation, School and Chair of Allergology and Clinical Immunology, University of Bari - Aldo Moro, Bari, Italy
2Dermatology Unit, Surgical, Medical and Dental Department of Morphological Sciences related to Transplant, Oncology and Regenerative Medicine, University of Modena and Reggio Emilia, Modena, Italy
3Division of Allergy and Clinical Immunology, Department of Medicine ASL Salerno, “Santa Maria della Speranza” Hospital, Battipaglia, Salerno, Italy
4Department of Internal Medicine and Clinical Pathology, Azienda Ospedaliera Universitaria Federico II, Naples, Italy
5Department of Biomedical Science and Human Oncology, University of Bari - Aldo Moro, Bari, Italy
6Division of Dermatology "U.O. Multizonale APSS", Santa Chiara Hospital, Trento, Italy

Manuscript received October 14, 2019; accepted for publication January 7, 2020.

Margarita Tomas Pérez
Department of Allergy
Hospital La Paz
Paseo de la Castellana, 261
28046 Madrid, Spain
E-mail: margui.tomas@gmail.com

Dupilumab was recently approved for the treatment of adults with moderate-to-severe atopic dermatitis (AD), for which current treatment options are limited [1]. Dupilumab binds to the IL-4Rα subunit and blocks the signaling of IL-4 and IL-13, thereby inhibiting the release of proinflammatory cytokines, chemokines, and IgE [2,3]. Although generally well-tolerated, high rates of unspecified conjunctivitis have been reported in patients on dupilumab [2-4].

This multicenter prospective observational study involved 15 secondary care centers as a task force for the Italian Society of Allergy, Asthma, and Clinical Immunology. The aim was to investigate the baseline factors associated with the incidence of dupilumab-induced conjunctivitis. Ninety-six patients with severe AD—defined as an Eczema Area and Severity Index (EASI) score ≥24—and with inadequate response to/ intolerance of cyclosporin A (CsA), or medically classified as unsuitable for CsA treatment, were enrolled and treated with a 600-mg loading dose and subsequent biweekly 300-mg injections of dupilumab for 16 weeks. During treatment, the investigators diagnosed, reported, and determined the severity and type of conjunctivitis (conjunctivitis; conjunctivitis, bacterial; conjunctivitis, viral; conjunctivitis, allergic; and

#The members of the Italian DADReL (Dupilumab Atopic Dermatitis in Real Life) Study Group are listed in the Acknowledgments
atopic keratoconjunctivitis [Medical Dictionary for Regulatory Activities preferred terms]) at baseline and at weeks 4, 8, 12, and 16. All patients with moderate-to-severe conjunctivitis were referred to an ophthalmologist.

The study protocol was approved by the principal ethics committee, and informed consent was obtained from all patients. To assess the risk of baseline characteristics being associated with a conjunctivitis event, a Cox regression time-to-event analysis was performed. Baseline factors were evaluated individually and in a multivariable model, including age class (<33 years vs ≥33 years) and sex. These factors were as follows: clinical scores (EASI, classified as above vs below the 75th percentile; Dermatology Life Quality Index [DLQI], classified as a small effect on quality of life [QoL] below 6, moderate effect on QoL up to 10, very large effect on QoL up to 20 and more than 20; Scoring Atopic Dermatitis [SCORAD], classified as above or below the 75th percentile; Patient-Oriented Eczema Measure [POEM], classified as mild when lower than 8, moderate up to 16, severe up to 24, and very severe more than 24; numerical rating scale [NRS] for sleep and NRS for pruritus, both classified as below and above the 75th percentile), IgE levels (classified as normal up to 100, from 100 to the 75th percentile, below the 75th percentile), eosinophil counts (classified as below or above 350), and family history of allergic conjunctivitis and history of conjunctivitis (both classified as present or not present). A stepwise selection procedure was used to improve the model fit and select variables associated with moderate-to-severe conjunctivitis events; a P value ≤.05 entry model was applied. The final model was adjusted for age class, sex, IgE (≤3637 vs >3637), and history of conjunctivitis. The goodness of fit was evaluated using R² and the C-index according to Pencina and D’Agostino [5].

Among the 96 patients invited to participate, 24 were diagnosed with conjunctivitis at baseline and were removed from the analysis. Among the remaining 72 patients, 29 (40.3%) were diagnosed with dupilumab-associated conjunctivitis during follow-up. This was mild in 18 patients (62%), moderate in 8 (27.6%), and severe in 3 (10.3%). Mean time to the first dupilumab-associated conjunctival event was 12 weeks (standard error, 0.58).

The cause of dupilumab-associated conjunctivitis is still unclear [4,8]. Patients with AD have a greater prevalence of ocular comorbidities than the general population [9], and administration of dupilumab for asthma or nasal polyposis

| Table. Summary of Conjunctivitis Events at Initiation of Treatment and During the Treatment Period in 96 Patients |
|---------------------------------------------------|---------------------------------------------------|---------------------------------------------------|
| **Conjunctivitis at Initiation of Dupilumab (n=24)** | **Incidence of Conjunctivitis During Treatment With Dupilumab** (n=29) | **Prevalence of Conjunctivitis During Treatment With Dupilumab (n=53)** |
| Conjunctivitis event, No. (%) | 24 (25.0%) | 29 (40.3%) | 53 (55.2%) |
| Conjunctivitis a | 3 (3.2%) | 22 (30.6%) | 25 (26.0%) |
| Allergic conjunctivitis | 17 (17.7%) | 2 (2.8%) | 19 (19.8%) |
| Atopic keratoconjunctivitis | 4 (4.1%) | 3 (4.2%) | 7 (7.3%) |
| Bacterial conjunctivitis | 0 (0%) | 1 (1.4%) | 1 (1.0%) |
| Viral conjunctivitis | 0 (0%) | 1 (1.4%) | 1 (1.0%) |

aThe incidence was calculated among the 72 patients who were not diagnosed with conjunctivitis at baseline.
bConjunctivitis in which the etiology remained unspecified.
has not been associated with higher rates of conjunctivitis [4]. Some authors hypothesize that both dupilumab- and AD-related mechanisms may be involved and that ocular or immune differences between patients with AD and other type 2 diseases might be considered [3]. Others have suggested that an increased eosinophil count after drug administration, which plays a part in the development of allergic eye disorders, could increase the risk of dupilumab-induced conjunctivitis [4,9]. Recent papers hypothesize that the IL-13 and/or IL-4 blocking effect might lead to the reduction of goblet cells and mucus production in a subpopulation of AD patients that may potentially result in irritative conjunctivitis [10,11]. This fact was confirmed when dupilumab was withdrawn [12]. The use of artificial tears during treatment with dupilumab might reduce the incidence of conjunctivitis/keratitis [6,13].

While limited by its relatively small sample size, short follow-up, and a lack of a control group, our study shows that patients with moderate-to-severe AD and a history of conjunctivitis seem to be at greater risk of developing dupilumab-associated conjunctivitis. Identifying associated risk factors at baseline may help to predict the onset of conjunctivitis during treatment with dupilumab. We recommend artificial tears in patients with AD treated with dupilumab to reduce the incidence of conjunctivitis and keratitis.

Acknowledgments

Italian DADRel (Dupilumab Atopic Dermatitis in Real Life) Study Group

1Dermatology and Venereology Private Practice, Gallipoli, Lecce, Italy; 2Dermatology and Venereology Private Practice Bari, Italy; 3Department of Internal Medicine and Clinical Pathology, Azienda Ospedaliera Ospedali Civili di Bari- Aldo Moro, Bari, Italy; 4Neumology Department, Sacro Cuore Hospital, Gallipoli, Lecce, Italy; 5Allergy Unit, Fondazione Policlinico A. Gemelli, “F. Miulli” Hospital, Acquaviva delle Fonti, Italy; 6Allergy Unit, Careggi University Hospital, Florence, Italy; 7Division of Allergy and Clinical Immunology, University of Florence, Florence, Italy; 8Dermatology and Venereology Private Practice, Bari, Italy; 9Dermatology and Venereology Private Practice Bari, Bari, Italy; 10Division of Allergy and Clinical Immunology, Unit of Internal Medicine, University of L’Aquila, L’Aquila, Italy; 11Department of Medicine and Otolaryngology, University of Bari, Italy; 12Section of Allergy and Clinical Immunology, Unit of Internal Medicine, University of Palermo, Scuola di Medicina e Chirurgia, Palermo, Italy; 13Section of Allergy and Clinical Immunology, Unit of Internal Medicine, University of Reggio Emilia, Modena, Italy; 14Immunology, G. D’Annunzio University, Chieti, Italy; 15Department of Ophthalmology, Studi di Palermo, Scuola di Medicina e Chirurgia, Palermo, Italy; 16Dipartimento Biomedico di Medicina Interna e Specialistica, Università degli Studi di Palermo, Scuola di Medicina e Chirurgia, Palermo, Italy; 17Department of Emergency and Organ Transplantation, School and Chair of Allergology and Clinical Immunology, University of Bari - Aldo Moro, Bari, Italy; 18“A. Perrino” Hospital, Brindisi, Italy; 19Allergology and Immunology Clinic, Operative Unit of Medicine, Policoro Hospital, Policoro, Matera, Italy.; 20Department of Clinical and Experimental Medicine, Unit of Internal Medicine, University of Florence, Florence, Italy; 21Dermatology and Venereology Private Practice Bari, Italy; 22Immunodlergology Unit, Careggi University Hospital, Florence, Italy; 23Dermatology and Venereology Private Practice Bari, Italy; 24Dermatology and Venereology Private Practice Bari, Barletta, Italy

Funding

The authors declare that no funding was received for the present study.

Conflicts of Interest

The authors declare that they have no conflicts of interests.

References

Manuscript received December 23, 2019; accepted for publication January 7, 2020.

Laura Bonzano
Dermatology Unit, Surgical, Medical and Dental Department of Morphological Sciences related to Transplant, Oncology and Regenerative Medicine, University of Modena and Reggio Emilia
Largo del Pozzo, 71
41125 Modena, Italy
E-mail: laurabonzano83@gmail.com


Daucus carota L. (carrot) is a vegetable that belongs to the Umbelliferae (Apiaceae) family. It is frequently implicated in food allergy and oral allergy syndrome, usually in association with other foods. Thus, hypersensitivity to carrot is commonly associated with allergy to Apiaceae species and sensitization to birch and mugwort pollens [1,2]. In southern Spain, allergy to Artemisia vulgaris is quite frequent, in contrast to allergy to Betula verrucosa. Nevertheless, few cases of rhinitis and asthma induced by carrot allergy have been reported [3,4]. We investigated the allergens involved in a case of occupational rhinoconjunctivitis induced by carrot.

A 38-year-old male cook diagnosed with allergic rhinitis and asthma due to mite and pollen had been treated successfully with subcutaneous immunotherapy. For the previous 3 years, the patient had developed facial contact urticaria, sneezing, rhinorrhea, and conjunctivitis within a few minutes of handling or cutting raw carrots, although he had previously tolerated both raw and cooked intake.

A skin prick test (SPT) was performed with a set of airborne and commercial food allergens, as well as native fresh foods. The result was positive (average wheal diameter ≥3 mm) to house dust mite, cat, dog, and pollens (grasses, Salsola, and Olea) and negative to Artemisia species and birch pollens, lipid transfer protein (LTP), profilin, and commercial extract of carrot. Native fresh food SPT was positive to carrot (peel and pulp) and celery and negative to parsley, anise, and dill. A rubbing test with fresh carrot was also negative.

Levels of specific IgE (sIgE) were determined using the ImmunoCap system (Thermo Fisher Scientific). A positive sIgE result (>0.35 kU A/L) was recorded for rPhl p 1 (0.44 kUA/L), nOle e 1 (10.10 kUA/L), nSal k 1 (61.60 kUA/L), Artemisia vulgaris (10.80 kUA/L), carrot (12.80 kUA/L), and celery (12.20 kUA/L). sIgE was negative for LTP (rPru p 3) and profilin (rPhl p 12).