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Review

Adverse effects of dupilumab in chronic rhinosinusitis with nasal polyps. Case report and narrative review

Effetti avversi di dupilumab nel trattamento della rinosinusite cronica con poliposi nasale

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SUMMARY

Herein we review the current literature on the adverse effects related to biological therapy with the monoclonal antibody dupilumab in patients with type 2 inflammation prevalent phenotype chronic rhinosinusitis with nasal polyps (CRSwNP). Our review shows that the side effects of dupilumab may be linked to the prevalent type 2 inflammation phenotype (asthma, dermatitis, CRSwNP). We also report the first case of cutaneous rash as a side effect of dupilumab in a patient with CRSwNP.

KEY WORDS: dupilumab, chronic rhinosinusitis with nasal polyps, type 2 inflammation, cutaneous rash, adverse effect

RIASSUNTO

La presente revisione della letteratura è incentrata sugli effetti collaterali correlati al trattamento con l'anticorpo monoclonale dupilumab, con particolare riferimento alla rinosinusite cronica con polipi nasali. La revisione mostra come gli specifici effetti avversi della terapia con dupilumab appaiano direttamente correlati con il fenotipo prevalente di infiammazione di tipo 2. Si riporta inoltre il primo caso clinico di comparsa di rash cutaneo a seguito di assunzione della prima dose di dupilumab in questa categoria di pazienti.

PAROLE CHIAVE: *dupilumab, rinosinusite cronica con polipi nasali, infiammazione di tipo 2, rash cutaneo, effetto avverso*

Introduction

The prevalence of chronic rhinosinusitis (CRS) in the world population is estimated at 11-15% [1] with an average of 11% in European countries [2]. CRS has significant impact on patients' quality of life (QoL) and inevitably leads to a burdensome effect on healthcare costs in addition to social-economic impact by reducing individual productivity [3-5].

The very recent introduction of targeted therapies based on the use of monoclonal antibodies has significantly modified and improved the outcomes of these patients [6].

Dupixent® (dupilumab, Sanofi Genzyme) is a fully human monoclonal antibody that acts on the alpha subunit of the interleukin-4 receptor (IL 4Rα) [7], and is capable of inhibiting the action of both IL-4 and IL-13 [8]. Its administration has been approved in the EU since October 2020 [9] for the treatment of severe CRS associated with nasal polyps (severe CRSwNP) [10,11]. Previous approval by the FDA for its use in severe asthma and atopic dermatitis date to 2018, and there is now substantial data in the literature on the adverse effects (AE) of subcutaneous treatment with dupilumab [8,12,13,14].

In CRSwNP, this therapeutic option is suitable for selected patients who have a type 2 inflammation pattern-related endotype. Among the different criteria for in-

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clusion in the treatment protocol, previous failure of therapy with topical nasal and systemic corticosteroids and/or recurrence of nasal polyposis after surgery should be present [15,16].
Clinical assessment and follow-up of patients is carried out through outpatient assessment using standardised questionnaires aimed at the evaluation of the patient's QoL, e.g. the 22-item Sino-Nasal Outcome Test (SNOT-22) and the Visual Analogue Scale (VAS), endoscopic criteria (Nasal Polyp Score, NPS), functional testing (with Sniffin' Sticks or University of Pennsylvania smell identification test, UPSIT) and radiological evaluation, such as the Lund-Mackay computed tomography (CT) score [10,11,17,18].
The use of biological therapy has shown consistent benefit on symptoms and QoL, in addition to improvement in endoscopic and radiological markers in patients with CRSwNP. However, its use is associated with several adverse effects [17,19-21].
Herein, we review the current literature on the different adverse effects of dupilumab in patients suffering from different type 2 inflammatory diseases and highlight the variety of clinical presentations among the different pathologies such as atopic dermatitis, asthma and CRSwNP. We focus on the current literature about adverse effects in patients with CRSwNP and report the first case of cutaneous rash as a side effect of dupilumab localised on the caudal part of the body in a patient with CRSwNP.

Materials and methods

A review of the relevant international literature was carried out using the Medline® and Embase® databases with the following search term:
"Dupilumab" [All Fields] AND (side effects [MeSH Terms] OR adverse effects [MeSH Terms]). Subsequently another search was performed using: (("Dupilumab" [Title/Abstract] AND "side effects" [Title/Abstract] OR "adverse effects" [Title/Abstract]) AND ("nasal polyps" [Title/Abstract] OR "rhinosinusitis" [Title/Abstract])).
References of retrieved articles were scrutinised for additional articles. Articles and book chapters published in English and French were included. Abstracts of all articles and book chapters were screened and selected according to relevance, followed by full reading of the papers.
AE events in the current case series of our institution were further reviewed. Furthermore, a literature review for dupilumab-related AE in atopic dermatitis and asthma treatment was also performed.

Adverse effects in CRSwNP

Several clinical studies have reported adverse effects related to the use of dupilumab in patients with CRSwNP. Furthermore, a major risk in developing side effects is described in comparison to the control group treated with placebo [10,17,22]. The most frequent are, respectively, nasopharyngitis, injection site reaction and headache [15,17,22-24]. Less frequently epistaxis, lack of improvement, or worsening of nasal polyps, arthralgia, asthma or worsening of asthma have been reported [21,25,26].
To the best of our knowledge there are no reported cases of increased eosinophilia or ophthalmological or dermatological manifestations in patients treated with dupilumab for exclusive CRSwNP [10,15,22,27,28].

Authors' experience - Case report

Among 20 patients treated in our institution with dupilumab since January 2021, a single adverse event (AE) emerged. The patient reporting the AE was a 50-year-old male patient, with a confirmed diagnosis of CRSwNP, who had undergone multiple Endoscopic Sinus Surgeries (ESS) in the previous years (the last in 2011). The patient's comorbidities included bronchial asthma (pulmonary function tests show a FEV_1 59%, FVC 93%, positive bronchial reversibility test with salbutamol and a fraction of nitric oxide exhalated (FeNO) of 63% with poorly controlled symptoms by inhalation therapy, intolerance to acetylsalicylic acid (ASA), polyposis of the stomach and gastric body, prick tests negative for inhalant allergic diathesis and no prior episodes of dermatitis.
The patient underwent ENT evaluation in March 2021 for recurrence of persistent hyposmia and chronic nasal bilateral obstruction that was non-responsive to oral and topical steroids. Endoscopic evaluation (OLYMPUS, ENDOEYE™ LF-V) provided evidence of complete nasal obstruction due to bilateral polypoid neoformations (NPS average score of 8).
During ENT evaluation, the SNOT-22 questionnaire was administered with a total score of 89/110; olfactometry using identification Sniffin' Sticks (Burghart®) scored 3/12 and 4-Phase rhinomanometry values of 0.22 to the right side and 0.72 on the left side were observed.
After evaluation of blood eosinophils (0.71 x 10^9/L, r.v. 0.00-0.50 x 10^9/L) and nasal cytology (presence of eosinophils: 12/hpf,) that confirmed the presence of type 2 lead inflammation, treatment with dupilumab (300 mg) was initiated in May 2021 and followed by one injection every two weeks.
The first follow-up was performed after 1 month of treatment; the patient reported clear subjective clinical improvement (SNOT-22: 10 points), improvement of the endoscopic nasal findings with NPS of 4 (2 + 2), performance

at the Sniffin' Stick test (Burghart®) with recognition of 14 of 16 items and rhinomanometry values of 1.06 cm H_2O/l/s on the right and 1.18 cm H_2O/l/s on the left.
However, the appearance of pruritus accompanied by a skin rash localised on the caudal surfaces of the body (mainly localised on the lower limbs and groin) appeared at 2 weeks after the first administration, 1 day after the second administration of dupilumab (Figs. 1A-C, 2). After administration of antihistamine therapy (bilastine, 20 mg BID) with only transient benefit, the patient was sent for dermatological evaluation with diagnosis of irritative dermatitis and confirmation of the current therapy with addition of topical skin therapy with emollients. No other adverse effects (conjunctival inflammation, nasopharyngitis, or injection site inflammation were present). Blood work showed an increase of eosinophilia (0.90 x 10^9/L, r.v. 0.00-0.50 x 10^9/L). Adverse event reporting to the national authorities was promptly undertaken.
In July 2021 (after 3 months of dupilumab therapy), due to the persistence of cutaneous rash and worsening of pruritus, and despite the current local and systemic therapy, treatment with dupilumab was interrupted.
After discontinuation, the patient reported rapid disappearance of the cutaneous manifestation and resolution of pruritus at one month after treatment discontinuation.

Adverse effects in atopic dermatitis (AD)

Atopic dermatitis is a relapsing inflammatory chronic disease [29]. It affects 3 to 10% of adults and 10 to 20% of children [30]. Dupilumab has shown encouraging results in the treatment of controlled moderate-to-severe forms of AD that are resistant to treatments such as phototherapy, oral corticosteroids and immunosuppressants [29,30]. In addition, dupilumab allows a substantial reduction of toxic effects in comparison with other therapies [29].
Treatment-emergent AEs of dupilumab therapy are defined according to the Medical Dictionary for Regulatory Activities (MedDRA).
The most frequently observed AEs can be divided into infectious and non-infectious. Among infectious AEs, nasopharyngitis, upper respiratory tract infections, conjunctivitis and Herpes virus skin infections have been reported. Injection-site reactions, exacerbation of AD, headache and allergic conjunctivitis are the main non-infectious side effects reported in the literature [29,31-33]. Moreover, rare AEs such as facial redness, alopecia, arthralgia [12,13,33,34], itching and urticarial-like rash typically localised in head and neck region have been described [35,36].
According to many studies, conjunctivitis seems to be the only specific side effect related to dupilumab in patients with AD [31,37]. According to Wollemberg et al. [37], bilateral conjunctivitis occurred in 25-50% of their patients with AD treated with dupilumab. However, the pathological mechanism is not fully understood. Indeed, prescription of biological therapy and ocular manifestations show a temporal but not causal relation [37].
Cutaneous manifestations have been reported as side effects during the use of dupilumab in patients with AD. These include, rash-like forms which have been described exclusively on the acral portions of the body (mainly face and upper limbs) [35]. No patient has shown involvement of caudal portions [35].

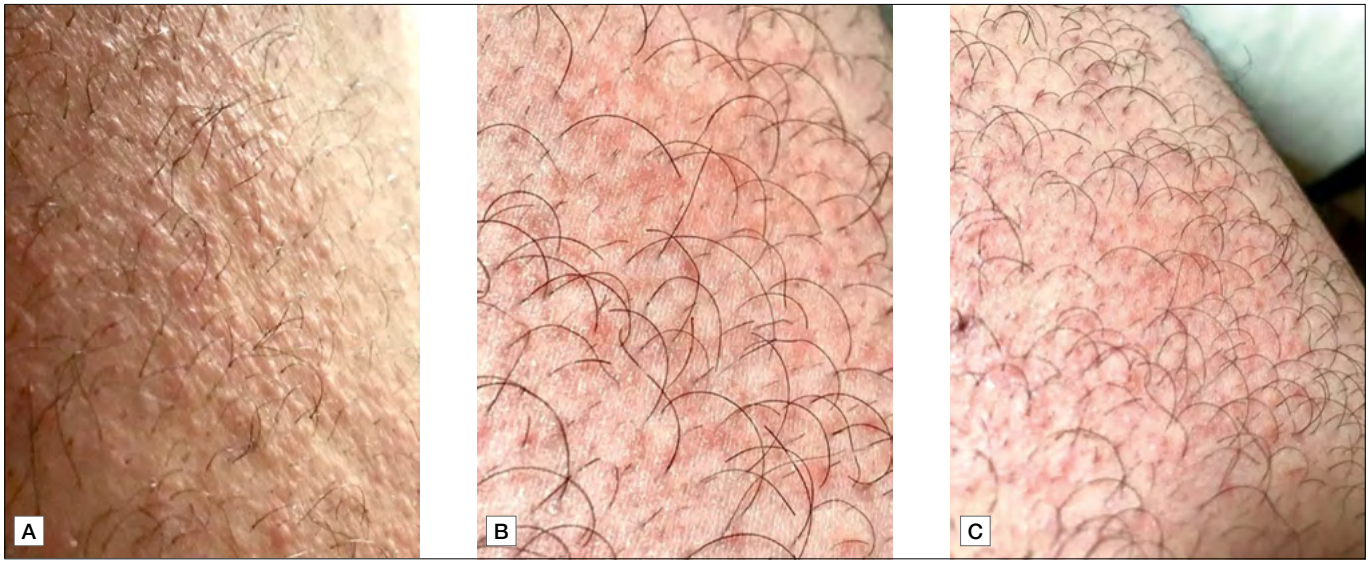

Figure 1A, B, C. Skin rash localised on the lower limbs and groin.

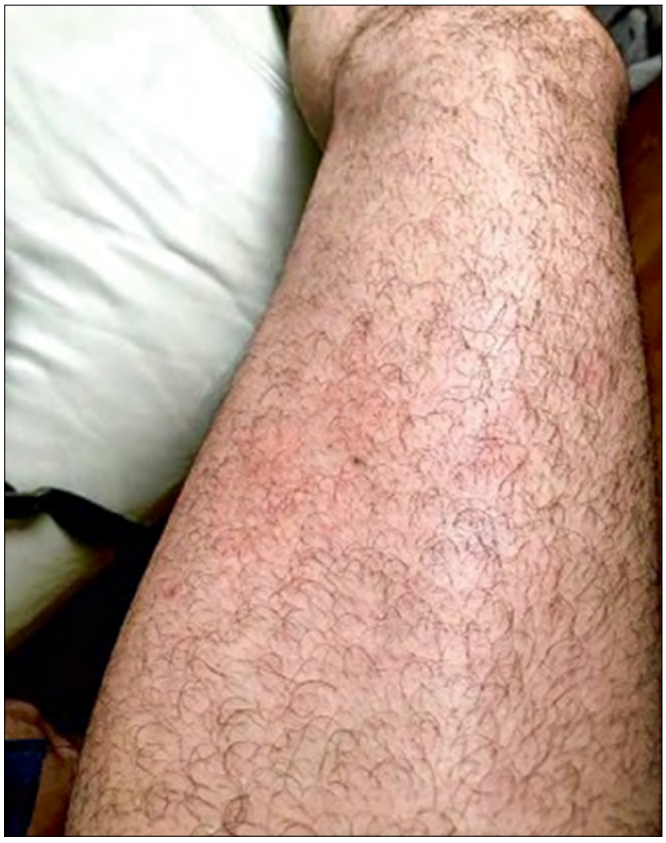

Figure 2. Urticarial-like rash localised on the lower limb.

Adverse effects in asthma

The efficacy and safety of dupilumab in treatment of asthma has been assessed by several studies [14,27,38-40]. Approximately 20% of patients with moderate-to-severe disease show uncontrolled symptoms with maximal standardised therapies [27].

The most frequent side effects, occurring in variable percentage of 5-13% in patients with asthma treated with dupilumab are injection-site reactions [14,27,38]. The appearance of blood eosinophilia may also be related to dupilumab therapy and is associated with an augmented risk of worsening of pre-existing hypereosinophilia symptoms (e.g. chronic eosinophilic pneumonia) [8,27,41].

In many studies upper respiratory tract (such as nasopharyngitis and sinusitis) and urinary infections are reported more frequently with dupilumab compared to placebo [27,38]. Influenza, headache and back pain are also mentioned as side effects of dupilumab therapy in asthmatic patients [14,27,38]. Conjunctivitis is rarely mentioned as an adverse effect in patients with asthma and no cause-effect relation has been established [27,38]. To the best of our knowledge, the appearance of skin manifestations (except for erythema localised in the injection site reactions) in dupilumab-treated asthma patients has not been reported.

Discussion

Biological therapies based on the use of monoclonal antibodies such as dupilumab show encouraging results in the treatment of comorbidities related to type 2 inflammation [21]. In patients with CRSwNP, dupilumab has been shown to improve symptom scores [17,42], eosinophilic and IgE blood counts [7], and endoscopic/radiological findings [17,21]. The recent introduction of biological therapy with dupilumab for CRSwNP was accompanied by different types of side effects in type 2 inflammation-related diseases. At present, the effort of several authors to standardise those AEs and assess the safety of dupilumab seems to show some shortcomings in terms of concordance and identification of specific AEs in patients with CRSwNP. The safety and efficacy of this therapy have been confirmed by many studies, but side effects in patients with CRSwNP are nonetheless poorly described in the literature. In the LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52 multicentre studies, the most commonly reported AEs were nasopharyngitis, lack of improvement of nasal polyps and asthma, headache, epistaxis and injection-site reactions [21]. Likewise, according to a meta-analysis by Chong et al. in patients with CRSwNP, there is a low and uncertain increase of the risk of developing nasopharyngitis compared to the placebo group [22]. The randomised, double-blind, placebo-controlled parallel-group study by Bachert et al. in 2016 was one of the few which investigated the side effects of dupilumab in CRSwNP with and without other comorbidities (50% of the sample suffered from asthma) with evidence of AEs in 25 of 30 patients in the placebo group and in all 30 patients in the dupilumab group. The most frequent AEs described were nasopharyngitis, injection site reactions (7 and 40%, respectively), and headache [17].

Although there is agreement about dupilumab-related AEs in patients with CRSwNP; there is a lack of studies focusing on the main side effects of therapy with dupilumab in patients with CRS with or without other comorbidities. Noticeably, different expressions of type 2 inflammation patterns seem to show distinct side effects, and in fact most of the cutaneous adverse effects described in the literature have been reported in patients with AD or other cutaneous type 2 inflammation manifestations [33]. The description of itching and urticarial-like rash is only referred in literature to patients with AD, as a side effect of dupilumab administration [33,36,43]. Deleuran et al. in their clinical trial stated that cutaneous side effects, such AD, should be included in the most common AEs in those patients [44].

The Food Drug Administration (FDA) [45] and Kim et al. [43] reported that the appearance of generalised urticaria is seen in < 1% of patients who received dupilumab and only in clinical trials on AD. Furthermore, it is interesting that these clinical features tend to appear exclusively on the acral portions of the body (trunk, upper limbs, face and neck), while in the literature no forms localised to the lower limbs and inguinal region have been described [35].

Our clinical case is the first to describe a lower limb dermatitis in a patient after the administration of dupilumab for CRSwNP. In our experience, only interruption of dupilumab therapy allowed for resolution of pruritus and skin rash, despite antihistamine treatment. It has to be noted that this single report of a patient with a skin AE in the context of CRSwNP is an exception to the general trend linking AE to the specific type 2 inflammation-related disease.

This review of the current literature on the safety of dupilumab highlights that different type 2 inflammation-related diseases seem to show different adverse effects. In addition, our review has shown that different studies focusing on the same phenotype of type 2 inflammation show no concordance in terms of AE reported.

Conclusions

Herein, we presented the first case report of a lower limb cutaneous side effect related to therapy with dupilumab for CRSwNP. Narrative review of the literature showed that the side effects of dupilumab may be specific to the prevalent phenotype of type 2 inflammation (asthma, dermatitis, CRSwNP) and further studies will be needed to establish which AEs are more likely in each subgroup and define their pathogenetic mechanisms.

Conflict of interest statement

The authors declare no conflict of interest.

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Authors' contributions

LN: study design, article search and selection, data extraction and drafting of the article. CR, FA and AMB: drafting of the article. AMS and CP: study design, critical revision of the article.

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