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Efficacy and Safety of Dupilumab Across Different Th2-Type-Mediated Diseases: A Real-Life Preliminary Experience

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Abstract: Background: Dupilumab, a fully human monoclonal antibody targeting the interleukin (IL)-4/IL-13 pathway, is able to dampen T helper (Th)2-mediated inflammation in several conditions characterized by this particular type of phlogosis. The aim of this study was to review the efficacy and safety of dupilumab treatment in conditions underpinned by Th2-type inflammation in a cohort of real-world patients referred to our outpatient clinic. Methods: Data from all patients with atopic dermatitis, chronic rhinosinusitis with nasal polyps, asthma, and other Th2-type-mediated inflammatory conditions treated with dupilumab were retrospectively reviewed. Results: Twenty-two patients were included in the study: 14 with atopic dermatitis, 5 with chronic rhinosinusitis with nasal polyps, 2 with asthma, and 1 with prurigo nodularis; some of the patients had more than one atopic condition. A complete response was observed in 13 out of 22 patients (59.1%); when partial responses were included in the analysis, the overall response rate was 86.4%. No adverse events were recorded, either locally or systemically. Total IgE levels dropped in all patients, in some cases reaching values close to those typically observed in nonatopic subjects. When eosinophilia was present at baseline, this also normalized during dupilumab treatment. Conclusions: Dupilumab was safe and effective across multiple conditions driven by Th2-type chronic inflammation; effective interference with the Th2-type pathway was inferred by the progressive reduction in serum total IgE levels, which reached the normal range in a fraction of patients, and by the reduction in peripheral blood eosinophil counts. Further studies in different Th2-mediated diseases are warranted.

Keywords: dupilumab; Th2-type inflammation; atopic dermatitis; chronic rhinosinusitis with nasal polyps; asthma; prurigo nodularis; IgE serum levels; eosinophils

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1. Introduction

Type 2 T helper (Th2) lymphocytes are known to be physiologically involved in orchestrating immune responses against helminths and in promoting mechanisms of tissue repair [1–5]. However, a dysregulated type 2 immunity may also contribute to the onset and maintenance of chronic inflammation underlying nearly all forms of atopic diseases, such as allergic asthma and rhinitis, and to the pathogenesis of fibrotic diseases [6–8]. Many of the pleiotropic effects exerted by Th2 lymphocytes, both physiologically and pathologically,

are mediated by the characteristic signature cytokines they secrete, i.e., interleukin (IL)-4, IL-5, and IL-13 [1–9]. Specifically, IL-4 and IL-13 are pivotal cytokines required for isotype switching in B cells, leading to the production of IgE by plasma cells; IL-5 is best known for its positive effects on eosinophil biology, resulting in activation, recruitment, and survival of these cells [2,3,9]. Atopic diseases, which can be considered as the result of a hyperreactive Th2-type immunity [4–9], are therefore characterized by elevated serum IgE levels and/or peripheral or tissue eosinophilia. Apart from eosinophils, other relevant effector cells involved in atopic diseases are mast cells and basophils [10–12]. These cells are equipped with high-affinity receptors for IgE and release the content of their granules in response to IgE cross-linking by allergens on the cell surface; in addition, they produce and secrete further mediators and cytokines, which amplify the inflammatory response [12,13]. Until a few years ago, treatment of atopic diseases was mainly based on different regimens of steroids and antihistamines, administered either systemically or topically; with the advent of therapeutic monoclonal antibody technology, a paradigm shift has occurred, particularly in the treatment of severe forms of atopic diseases, owing to the availability of biologic therapies able to inhibit specific molecular targets crucially involved in the pathogenesis of Th2-mediated diseases [8,14–16]. Among the therapeutic monoclonal antibodies currently approved for the plethora of atopic diseases characterized by dysregulated Th2-type immunity, dupilumab, a fully human monoclonal antibody specific for the α chain of the IL-4 receptor (which is also shared by the IL-13 receptor), holds an important place in therapy because it antagonizes an early step in the inflammatory cascade (inhibition of the effects of IL-4 and IL-13) and because of the multiple indications it has obtained over recent years [17–20]. Starting first with atopic dermatitis, in fact, dupilumab then received approval for several other diseases characterized by evidence of underlying Th2-mediated chronic inflammation, namely, asthma, chronic rhinosinusitis with nasal polyps (CRSwNP), prurigo nodularis, eosinophilic esophagitis, and chronic obstructive pulmonary disease (COPD) [21–27]. The aims of this work were therefore to assess the real-world efficacy and safety of dupilumab in diseases sharing similar pathogenetic pathways, e.g., asthma, atopic dermatitis, and chronic rhinosinusitis with nasal polyps. The behavior of surrogate markers of atopy, such as total IgE serum levels and peripheral blood eosinophil counts, was regularly monitored before and during dupilumab therapy and represented a secondary aim of the study.

2. Patients and Methods

2.1. Patients

The medical records of patients who were prescribed dupilumab for a moderate/severe Th2-mediated condition unsatisfactorily controlled by conventional therapies were retrospectively reviewed. Briefly, data were available for 22 patients, whose main condition was as follows: atopic dermatitis (total 14), chronic rhinosinusitis with nasal polyps (total 5), asthma (total 2), and prurigo nodularis (total 1); while some of the patients suffered from more than one atopic condition, dupilumab was prescribed for the most bothersome manifestation. The characteristics of the patients are summarized in Tables 1–3. Disease severity was graded according to validated clinical tools before and during dupilumab treatment. Specifically, SCORAD (SCORing Atopic Dermatitis [28]), SNOT-22 (Sino-Nasal Outcome Test-22 [29]), pulmonary function test results, and IGA-Prurigo (Investigator Global Assessment for Prurigo) [30] results were used to categorize and monitor the severity of atopic dermatitis, CRSwNP, asthma, and prurigo nodularis, respectively. Briefly, SCORAD results, ranging from 0 to 103, were categorized as follows: <12 clear/almost clear skin; 12–25 mild disease; 26–50 moderate disease; >50 severe disease [28]. SNOT-22 results, ranging from 0 to 110, were interpreted as follows: 8–20 mild disease; 21–50 moderate

disease; >50 severe disease [29]. GINA guidelines were used to classify asthma severity [31]. Finally, IGA-Prurigo allowed definition of stage and activity on a scale from 0 to 4 (grade 0: clear; grade 1: almost clear; grade 2: mild; grade 3: moderate; grade 4: severe) [30]. Patients were considered eligible for biological therapy if they obtained scores consistent with moderate to severe disease using the above validated clinical tools, were dependent on chronic administration of oral/parenteral steroids for disease control despite maximal standard specific therapy, and/or were intolerant of or incapable of adhering to conventional treatments. Exclusion criteria were limited to concomitant active acute or chronic infections requiring specific treatment, ongoing biologic therapy for other associated systemic conditions, or coexisting psychiatric diseases potentially able to affect treatment compliance. All patients were assessed every three months for the first year following dupilumab initiation, then once every six months, in case of stable disease control. Decision on whether to continue or withdraw dupilumab treatment was taken at an extra 16-week follow-up visit. Total serum IgE levels and eosinophil counts were also assessed at each follow-up visit.

Table 1. Pre-treatment characteristics of the whole patient population (total 22).

Gender, M/F	**12/10**
Age	
mean ± standard deviation	33.6 ± 14.5
median	30
Total serum IgE, IU/mL *	
mean ± standard deviation	2362 ± 3003
median	822
Circulating eosinophil counts, cells/µL	
mean ± standard deviation	462.2 ± 221.7
median	423
Allergic phenotype	
AD, AR	4 patients
AD, *AR*, *AA*	5 patients
AD, *AR*, *FA*	1 patient
AD, *AR*, *ACD*	2 patients
AD, *AR*, *AA*, *FA*	2 patients
CRSwNP	3 patients
CRSwNP, *AA*	1 patient
CRSwNP, ***AA***	1 patient
CRSwNP, *AD*	1 patient
AR, ***AA***	1 patient
PN, *ACD*	1 patient
Disease severity	
SCORAD	
mean ± standard deviation	59.9 ± 11
median	61.8
SNOT-22	
mean ± standard deviation	45.2 ± 8.2
median	50
FEV1	
mean ± standard deviation	68 ± 1.4
median	68
IGA-Prurigo	4/4 stage
	4/4 activity **

* normal values up to 100 IU/mL. ** only one patient; the values reported are individual. Abbreviations: ACD, allergic contact dermatitis; AD, atopic dermatitis; AR, allergic rhinitis; AA, allergic asthma; CRSwNP, chronic rhinosinusitis with nasal polyps; F, female; FA, food allergy; FEV1, Forced Expiratory Volume in 1 s; IGA-Prurigo, Investigator Global Assessment for Prurigo; M, male; PN, prurigo nodularis; SCORAD, SCORing Atopic Dermatitis; SNOT-22, Sino-Nasal Outcome Test-22. Bold type indicates the condition primarily treated with dupilumab.

2.2. Dupilumab Schedule

Dupilumab was administered according to the licensed schedule [32]. Specifically, atopic dermatitis and asthma patients were started on 600 mg subcutaneously (s.c.) on day 1 and then proceeded with 300 mg every 14 days; CRwNP patients were started on 300 mg from the beginning of the treatment and were recommended to re-inject the drug every two weeks. The only patient with prurigo nodularis was treated empirically, according to the atopic dermatitis schedule (which is now the currently approved dose for prurigo nodularis as well [32]), because at the time of enrollment dupilumab had not yet been approved for such a condition, the patient thus receiving an off-label therapy. The complete description for this patient is reported elsewhere [33].

Table 2. Pre-treatment characteristics of the patients with Th2-mediated inflammatory skin involvement (14 atopic dermatitis + 1 prurigo nodularis).

Gender, M/F	**6/9**
Age	
mean ± standard deviation	34.5 ± 14.5
median	30.5
Total serum IgE, IU/mL *	
mean ± standard deviation	3298.7 ± 3131.4
median	2108.5
Circulating eosinophil counts, cells/μL	
mean ± standard deviation	451.5 ± 245.9
median	411.5
SCORAD index **	
range	38.2–82.3
Associated comorbidities	
Allergic rhinitis	14 patients
Allergic asthma	7 patients
Food allergy	3 patients
Chronic rhinosinusitis with nasal polyps	1 patient
Allergic contact dermatitis	2 patients

* normal values up to 100 IU/mL. ** SCORAD interpretation: <12 clear/almost clear skin; 12–25 mild disease; 26–50 moderate disease; >50 severe disease [28].

Table 3. Pre-treatment characteristics of the patients with Th2-mediated inflammatory respiratory involvement.

Gender, M/F	**6/1**
Age	
mean ± standard deviation	35.6 ± 18.1
median	26
Total serum IgE, IU/mL *	
mean ± standard deviation	333.5 ± 436
median	139
Circulating eosinophil counts, cells/μL	
mean ± standard deviation	457.8 ± 146.2
median	530
SNOT-22 **	
range	34–50

Table 3. *Cont.*

Gender, M/F	6/1
FEV1 *range*	 67–69
Associated comorbidities *Atopic dermatitis*	 1 patient

Abbreviations: SNOT-22, Sino-Nasal Outcome Test-22; FEV1, Forced Expiratory Volume in 1 s. * normal values up to 100 IU/mL. ** SNOT-22 interpretation: 8–20 mild disease; 21–50 moderate disease; >50 severe disease [29].

2.3. Laboratory Investigations

Total serum IgE levels and peripheral blood eosinophil counts were measured before starting dupilumab administration and at 3-month intervals thereafter, using standard hospital laboratory kits and instrumentation; at the end of the first year of follow-up, patients who achieved sustained benefit underwent these serial measurements every 6 months.

2.4. Safety Assessment

All patients received the first dupilumab injection in the outpatient clinic and were kept under surveillance for the following two hours, to assess possible local or systemic reactions to the therapeutic monoclonal antibody. In case of no adverse events, the patients were allowed to continue the treatment at home. All patients were asked to record any unwanted side effect possibly associated with dupilumab therapy during home treatment with the monoclonal antibody.

2.5. Statistical Analysis

All comparisons were made with Student's *t*-test for paired variables.

3. Results

3.1. Patients

The mean ± standard deviation and median duration of therapy were 24.8 ± 16.6 and 28 months, respectively. Within this time frame, the overall response rate to dupilumab was 86.4% (19 of 22 patients), when summing up the complete plus partial responses. Only 3 patients did not report significant benefit: 2 patients with atopic dermatitis, who did not obtain clearance of the disease on the face, around the eyes, and on the neck, requiring a switch to Janus kinase inhibitor therapy (baricitinib), with subsequent complete remission; and 1 patient with CRwNP, whose SNOT-22 remained substantially unchanged after 9 months of dupilumab therapy. The only patient with prurigo nodularis also achieved a complete response (IGA-Prurigo 0/4 for stage and 0/4 for activity); details of the disease behavior during dupilumab treatment are decribed elsewhere [33]. All complete responders reported a significant benefit after the first month of treatment, and the response was complete by the 16th week of dupilumab administration. Allergic comorbidities (Tables 1–3) were relieved as well, with most of the patients (54.5%, 12 out of 22 patients) stopping anti-allergic drugs (mainly antihistamines) taken for comorbid Th2-mediated diseases. Figure 1 summarizes the results obtained in the whole population and according to the specific disease treated with dupilumab; Figure 2 represents examples of successful treatment responses in atopic dermatitis patients.

Table 4 reports the outcome in terms of the clinical scores in the study population; basically, dupilumab allowed patients to obtain a significant benefit in each subgroup of Th2-mediated diseases, with marked reductions in disease severity. Figures 3 and 4 show the behavior of the pertinent clinical score in detail for each patient.

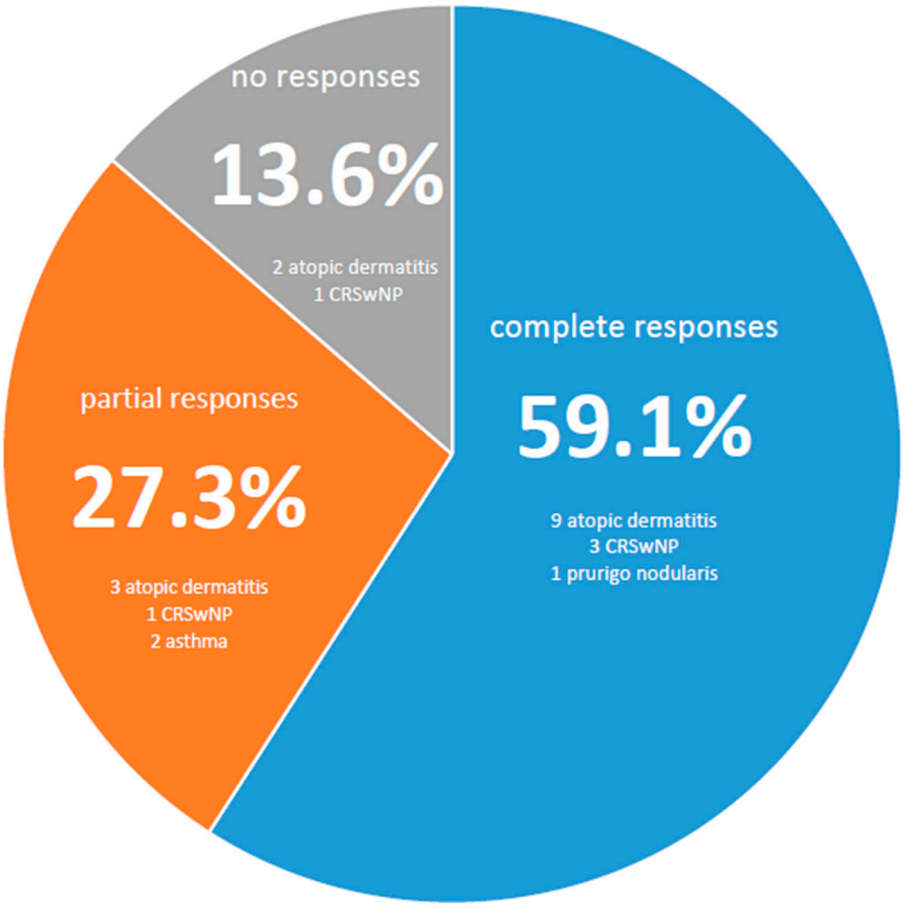

Figure 1. Overall and disease-specific response rates to dupilumab after a median treatment duration time of 28 months.

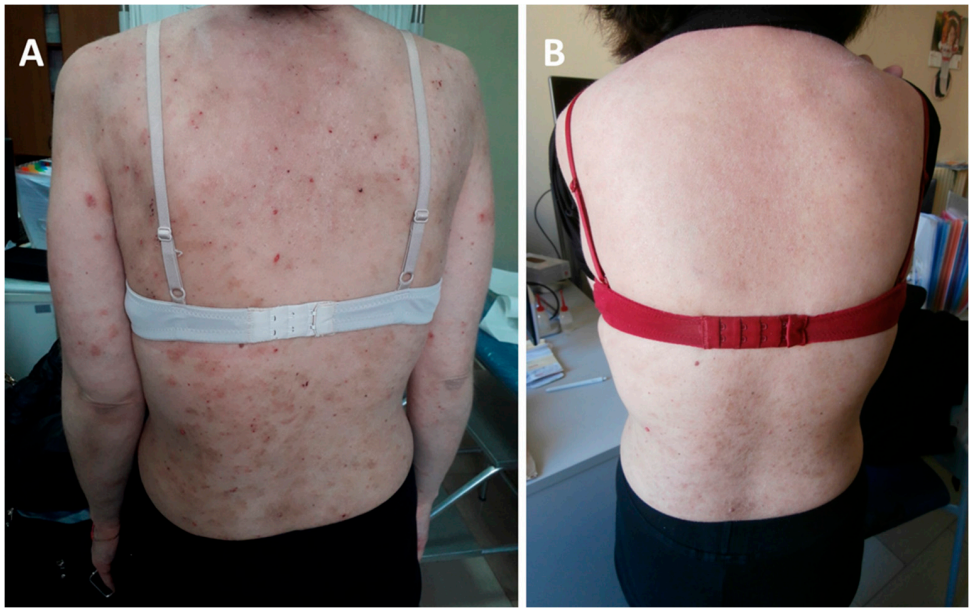

Figure 2. *Cont.*

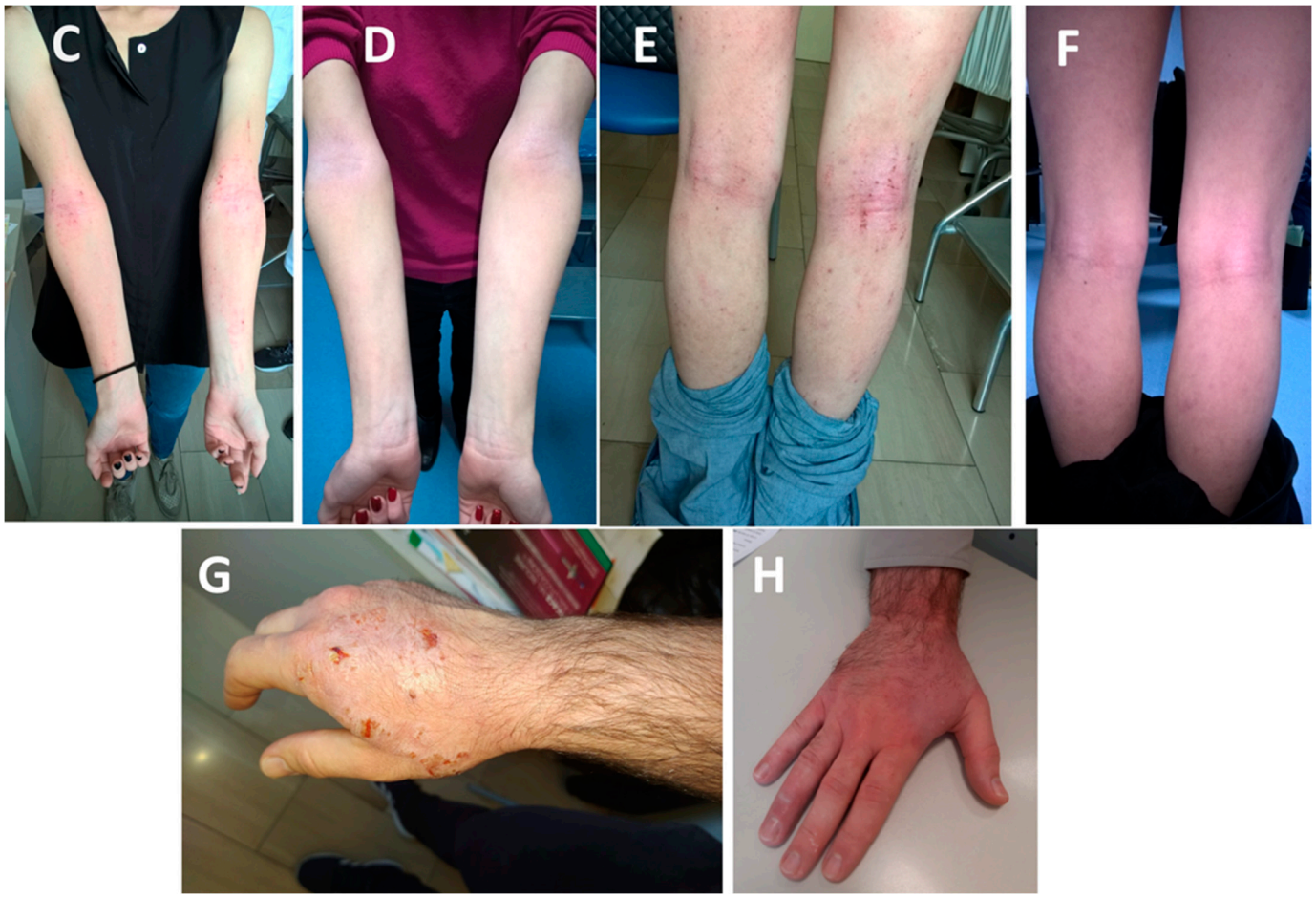

Figure 2. Representative examples of complete responses to dupilumab in atopic dermatitis patients. (**A**,**C**,**E**,**G**): pre-dupilumab treatment; (**B**,**D**,**F**,**H**): during dupilumab treatment. Eczema, excoriations, crusting, and lichenification were no longer visible following implementation of biologic therapy.

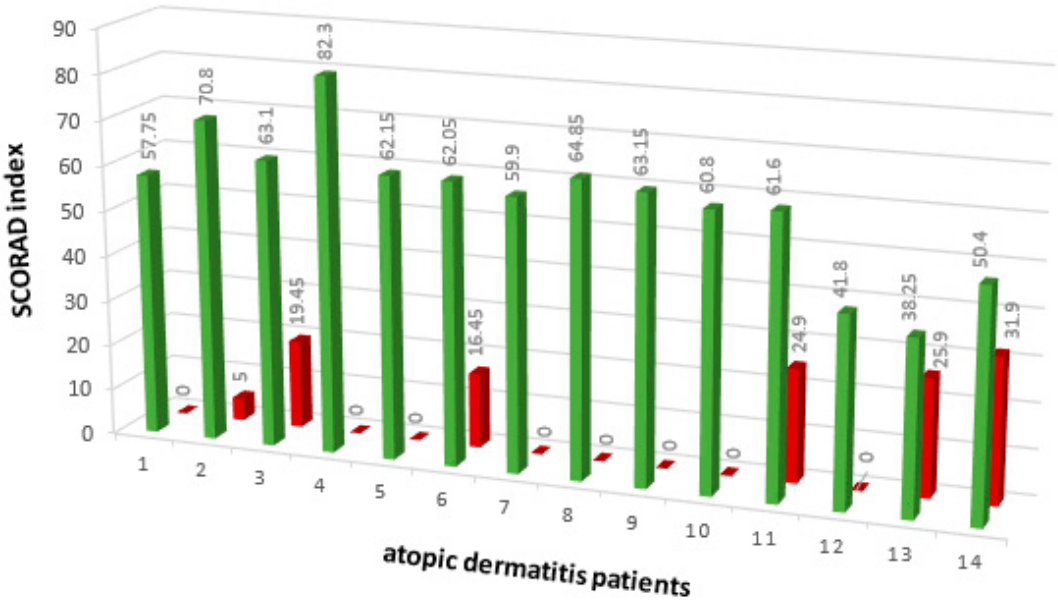

Figure 3. Effects of dupilumab treatment (median time 24 months) on SCORAD individual values (atopic dermatitis patient subgroup). Each number (1–14) corresponds to an individual patient. The green columns correspond to pre-treatment values, the red columns indicate SCORAD scores obtained during dupilumab treatment. Individual values are specified on top of each column.

Table 4. Outcome of clinical scores after implementation of dupilumab treatment.

CLINICAL SCORE		*p*
SCORAD		
pre-dupilumab	during dupilumab	<0.0001
59.9 ± 11 (mean ± standard deviation)	*8.8 ± 12.1 (mean ± standard deviation)*	
61.8 (median)	*0 (median)*	
SNOT-22		
pre-dupilumab	during dupilumab	0.0009
45.2 ± 8.2 (mean ± standard deviation)	*13.8 ± 11.2 (mean ± standard deviation)*	
50 (median)	*10 (median)*	
FEV1		
pre-dupilumab	during dupilumab	NA
68 ± 1.4 (mean ± standard deviation)	*75.5 ± 2.1 (mean ± standard deviation)*	
68 (median)	*75.5 (median)*	
IGA-Prurigo *		
pre-dupilumab	during dupilumab	NA
stage 4/4	*stage 0/4*	
activity 4/4	*activity 0/4*	

Abbreviations: FEV1, Forced Expiratory Volume in 1 s; IGA-Prurigo, Investigator Global Assessment for Prurigo; NA, not applicable; SCORAD, SCORing Atopic Dermatitis; SNOT-22, Sino-Nasal Outcome Test-22. * SCORAD interpretation: <12 clear/almost clear skin; 12–25 mild disease; 26–50 moderate disease; >50 severe disease [28]. SNOT-22 interpretation: 8–20 mild disease; 21–50 moderate disease; >50 severe disease [29]. * only one patient; the values reported are individual.

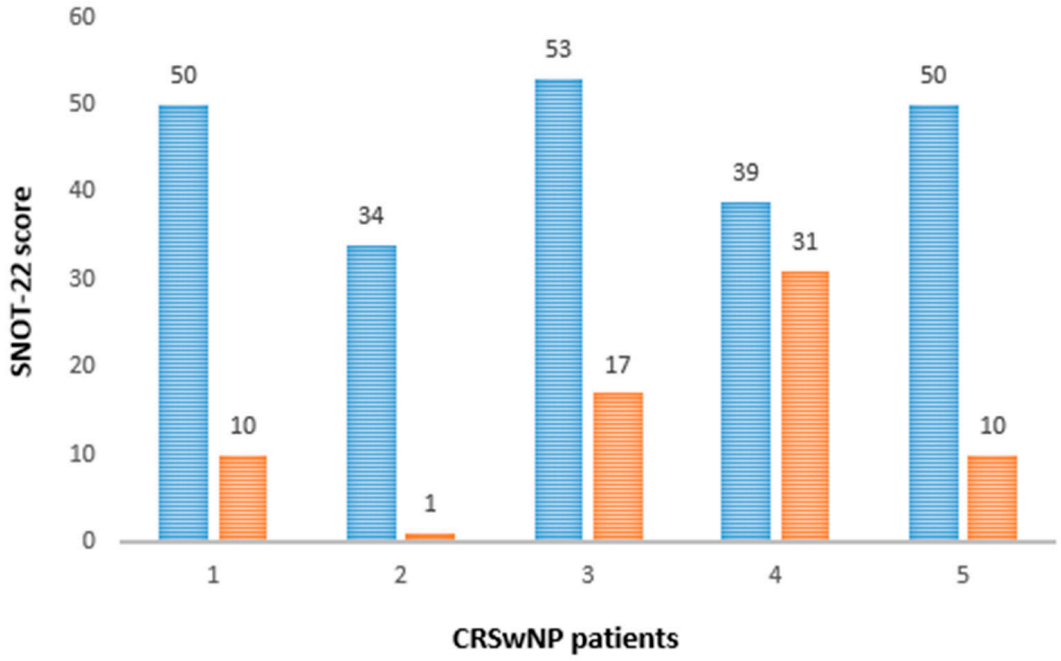

Figure 4. Effects of dupilumab treatment (median time 28 months) on SNOT-22 individual values (CRSwNP patient subgroup). Each number (1–5) corresponds to an individual patient. The blue columns correspond to pre-treatment values; the orange columns indicate SNOT-22 scores obtained during dupilumab treatment. Individual values are specified on top of each column.

Notably, most patients with atopic dermatitis obtained complete skin clearance, while patients achieving partial responses had, nonetheless, their disease downgraded to a mild condition. Although patient no. 11 and no. 13 depicted in Figure 3 achieved SCORAD results consistent with mild disease, they were considered unresponsive because skin lesions persisted unchanged on the head/neck, still causing embarrassment to the pa-

tients, thus forcing them to ask for alternative drugs in a further attempt to obtain disease clearance. The remaining patients with partial responses (nos. 3, 6, and 14) were satisfied with the results obtained and wished to continue the treatment; patient no. 2 achieved nearly complete skin clearance. Consistently, remarkable reductions in itch visual analog scores (on a scale from 0 to 10, with 0 = no itch and 10 = worst itch) were recorded (pre-dupilumab vs. 16-week follow-up scores: 9.0 ± 1.0/9.0 and 1.6 ± 2.6/0 mean ± standard deviation/median, respectively, $p < 0.0001$), with complete responders reporting no itch at all and cessation of scratching behaviors within 1–3 months of dupilumab treatment.

With regard to patients with respiratory involvement, CRSwNP subjects no. 1, 2, and 5 (Figure 4) were considered complete responders because symptoms no longer bothered the patients and reliever drug use was minimal or absent; only patient no. 4 reported no benefit at all. Patient no. 3 was satisfied with the clinical response and is still under treatment. Accordingly, patients with asthma, although still showing suboptimal results on pulmonary function tests (Table 4), reported significant improvements in subjective symptoms and are thus still on monoclonal antibody therapy.

3.2. Behavior of Surrogate Markers of Atopy During Dupilumab Treatment

Interestingly, all patients showed a progressive decline in serum total IgE levels, with values almost reaching those of nonatopic patients in at least 36.4% of patients. Figure 5 shows the significant reduction in the whole patient population. Figure 6 depicts the slow but steady decline of serum IgE levels over time in representative patients. The effect was most striking in atopic dermatitis patients, whose pre-treatment serum levels were exceedingly higher than normal values; notably, in these patients, reductions in total serum IgE levels were associated with progressive healing of skin lesions, abatement of itch scores, and cessation of scratching behaviors, suggesting a crucial role for hypersensitivity reactions in atopic dermatitis pathogenesis.

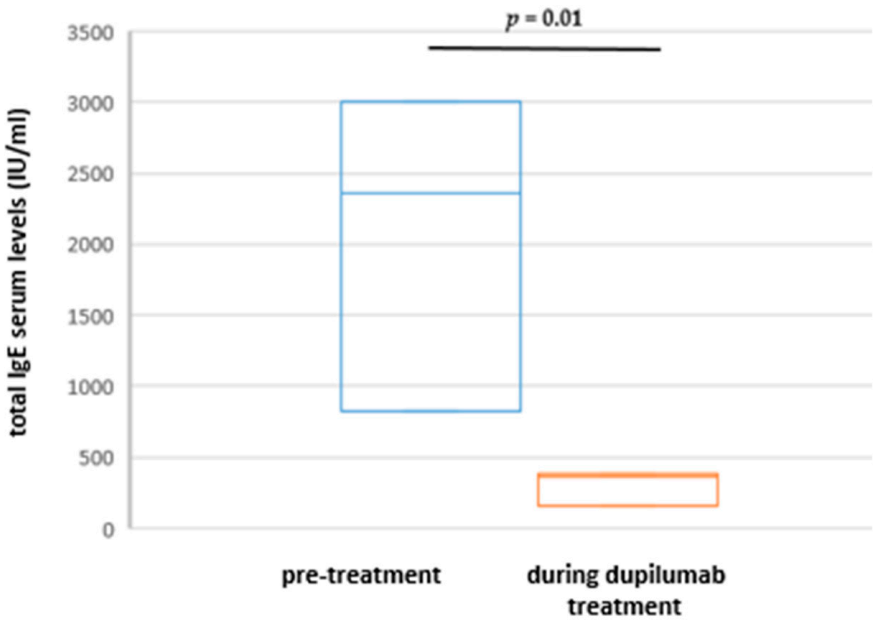

Figure 5. Effects of dupilumab treatment on serum total IgE patients. The upper line, the transverse line, and the bottom line of each box plot represent the standard deviation, the mean, and the median of serum total IgE levels of the whole study population, respectively (blue box: pre-treatment values; orange box: follow-up values, median time 28 months).

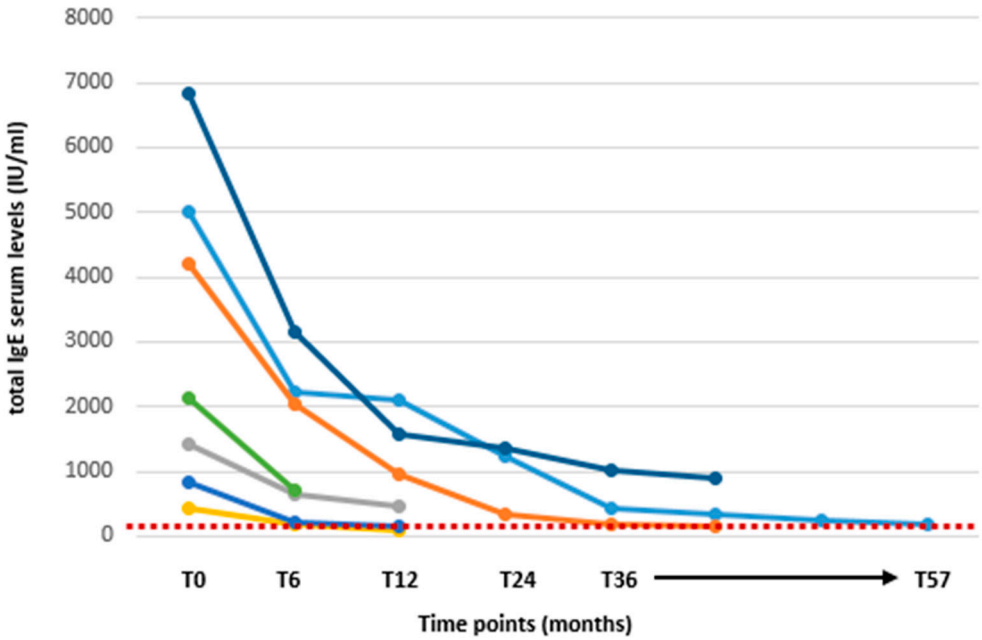

Figure 6. Behavior of total IgE concentrations (IU/mL) in 7 representative patients showing markedly elevated baseline (i.e., pre-treatment) serum levels, over a median dupilumab treatment time of 28 months. The red dotted line represents the upper limit of normal serum IgE levels (100 IU/mL). Notably, IgE declined into the normal range with time in some of the patients, regardless of pre-treatment serum levels.

Accordingly, individual patients with eosinophilia had their peripheral blood eosinophil counts returning into the normal range during dupilumab treatment. Since only 8 out of 22 patients showed eosinophilia before starting dupilumab, means and medians did not significantly differ on statistical analysis (pre-treatment mean ± standard deviation and median: 462.23 ± 221.7 and 423, respectively; during dupilumab therapy: mean ± standard deviation and median 405.4 ± 412 and 201, $p = 0.62$).

3.3. Adverse Events

No adverse events were recorded, either locally at the injection site or systemically, throughout the whole follow-up time.

4. Discussion

This study shows the effectiveness and safety of dupilumab in the treatment of different Th2-mediated diseases in real-life patients. The versatility of dupilumab is due to its mechanism of action, since central to Th2-mediated inflammation is the pivotal role played by IL-4 and IL-13 [3,9], whose signaling pathway is inhibited by the therapeutic monoclonal antibody [17–19]. Indeed, different atopic diseases, e.g., hay fever, allergic asthma, and food allergy, essentially differ according to the target organ involved by Th2-mediated inflammation, but the pathogenic pathway is basically the same [6–8]. Accordingly, we observed more than satisfactory responses using dupilumab in different Th2-mediated diseases, regardless of the target organ involved by allergic inflammation. Moreover, patients suffering from more than one atopic condition (e.g., combinations of atopic dermatitis and rhinitis or asthma) had all of their comorbid allergic conditions well-controlled by dupilumab as well.

IL-4 and IL-13 are needed by B cells to operate the isotype switch towards IgE [34,35]. As a result of their inhibition by dupilumab, we observed declining IgE serum levels during treatment, with some patients even showing IgE titers overlapping those of nonatopic

subjects. This observation, coupled with the evidence of eosinophil count normalization during treatment, supports the notion that dupilumab may even revert the biochemical atopic signature, at least as long as treatment is continued. Interestingly, in our patient series, several atopic dermatitis patients showed remarkably high serum total IgE levels before starting dupilumab therapy; notwithstanding, dupilumab was able to progressively inhibit IgE synthesis, regardless of the "intensity" of the atopic signature. In this regard, it differs from omalizumab, for instance, whose IgE neutralization activity is optimal only within a definite range of serum IgE levels [36–39].

The mechanism of action of dupilumab has important therapeutic implications. Although this monoclonal antibody has already received indication for other Th2-mediated inflammatory diseases, namely eosinophilic esophagitis and COPD, it has still the potential to positively affect the outcome of other conditions sharing the same pathogenic pathway [40]. For instance, dupilumab may theoretically be used to treat food allergy [41] or the most feared manifestation of allergic reactions, namely anaphylaxis [42–44]. Studies are ongoing to assess whether dupilumab may hold a significant place in therapy in other Th2-mediated inflammatory conditions.

Although several side effects have been reported during dupilumab treatment [45–49], mainly in very large series such as those of clinical trials, none of our patients complained of undesired effects possibly linked to the use of the biologic drug. Conjunctivitis, nasopharyngitis, transient eosinophilia, and injection site reactions have mainly been described during the registration trials and in real-life clinical practice; however, most of the side effects reported thus far have always been deemed to be mild and rarely have they led to discontinuation of dupilumab [45–49]. The absence of side effects, in our experience, is not surprising, given the excellent tolerability profile of the drug and likely because of the small number of patients treated with dupilumab thus far, when compared to the very large numbers of subjects enrolled in clinical trials and included in post-marketing registries.

It should be noted that our patient population consisted of relatively young people. Indeed, the median age of the whole cohort was 30 years, and it did not substantially differ when patients were analyzed according to the type of disease (median age of patients with skin involvement: 30.5 years; median age of patients with respiratory involvement: 26 years); thus, it is unclear whether the same response rates and the absence of adverse events may also be recorded in older patients, who may suffer from age-related comorbidities, are usually on multiple medications, and display a different immune reactivity.

This study has some limitations, which can be mainly recognized in the relatively small number of patients and its retrospective design. In addition, it may be argued that no control group was used for dupilumab-treated patients; actually, the same patients served as both controls and the intervention group (i.e., before and during therapy), because of ethical issues arising in case of exclusion from treatment of patients with severe Th2-mediated conditions, despite the approval and availability of a "game-changer" drug, and due to the fact that this study was not conceived as a clinical trial. On the other hand, strengths of the study are the inclusion of real-life patients, the relatively long follow-up time (some patients have been on uninterrupted treatment for nearly 5 years now), the provenience of patients from the same geographic area, which ensured patient homogeneity from an environmental and genetic background point of view, and the documentation of the reversal of the biochemical atopy signature during treatment.

5. Conclusions

Dupilumab was safe and effective in patients with a variety of Th2-mediated diseases and was able to reverse the atopic phenotype as long as it was administered. Quality of life

was markedly improved in all patients. No undesired effects were recorded throughout the follow-up.

Author Contributions: Conceptualization, C.R. and E.A.; methodology, C.R., D.C. and E.A.; validation, C.R., D.C. and E.A.; formal analysis, C.R., D.C., M.E.C. and E.A.; investigation, C.R., D.C., M.E.C. and E.A.; data curation, C.R., D.C., M.E.C. and E.A.; writing—original draft preparation, C.R.; writing—review and editing, C.R., D.C., M.E.C. and E.A.; supervision, C.R. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and its later amendments. Because of its retrospective nature, formal ethics committee consent was not required as all of the procedures being performed were part of routine care.

Informed Consent Statement: All patients gave their consent for anonymous use of clinicopathological data and pictures for scientific purposes.

Data Availability Statement: Raw data are available upon reasonable request from the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest.

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