Hypereosinophilia during dupilumab treatment in patients with chronic rhinosinusitis with nasal polyps*

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Abstract

Background: Increased blood eosinophil count (BEC) is common in patients under dupilumab treatment for chronic rhinosinusitis with nasal polyps (CRSwNP). This study investigated the prevalence and consequences of hypereosinophilia and to help define patients at risk.

Methods: Real-life, prospective observational cohort study of patients treated with dupilumab for severe CRSwNP. Eligible patients were adult and biological-naïve (N=334). All BEC values at baseline and during treatment were reported.
Patients with a follow-up of ≥ 1 year were included to define patients at risk for hypereosinophilia by comparing baseline BEC values (N=218). Furthermore, clinical characteristics and therapeutic consequences for patients with BEC ≥ 3.0 were noted.

Results: Hypereosinophilia developed in a minority of patients, with a peak at week 12 (16.2% with BEC ≥ 1.5, and 1.7% ≥ 3.0) in cross-sectional analysis. BEC ≥ 1.5 developed in 28.9% and BEC ≥ 3.0 in 4.6% of cases with a minimal 1-year follow-up. Baseline BEC was significantly higher for patients developing BEC ≥ 1.5 and BEC ≥3.0, with an optimal cut-off point of 0.96 to predict developing BEC ≥ 3.0.

Conclusions: Blood eosinophil count (BEC) ≥ 1.5 is transient and usually abates with no therapeutic interventions and BEC ≥ 3.0 is rare. Hypereosinophilic syndrome did not occur and switching to a different biological was rarely employed. A baseline BEC of ≥1.0 can be a reason for extra caution.

Key words: biological therapy, chronic rhinosinusitis, dupilumab, eosinophils, nasal polyps

Introduction

Chronic rhinosinusitis (CRS) is a disease of the nose and paranasal sinuses defined by symptoms (nasal obstruction and/or rhinorrhoea combined with smell loss and/or facial pain/pressure) and signs (inflammatory changes in the middle meatus visible with nasal endoscopy or radiographic imaging) lasting at least 12 weeks [(1)]. Based on the endoscopic appearance of nasal polyps, CRS is divided between those with nasal polyps (CRSwNP) and those without (CRSsNP). This classification has been updated in the latest edition of the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS2020), where the type of CRS is described as being primary or secondary to underlying disease, with a certain anatomical distribution (localized or diffuse) and a dominant inflammatory endotype or underlying mechanism [(1)]. As such, in Western countries CRSwNP is usually primary diffuse type 2 CRS.

CRS has a prevalence of around 6% in the general population; CRSwNP has an estimated prevalence of 2-4% and imposes a heavy burden, both on patients individually, and on society as a whole [(2-5)]. Oftentimes, patients are struggling to attain or retain disease control despite appropriate medical therapy (nasal

rinsing, intranasal corticosteroids), oral corticosteroids and/or endoscopic sinus surgeries. A small portion of patients develops severe and uncontrolled CRSwNP [6]. For a few years, biological add-on therapy has become available to treat these patients. The first to be registered was dupilumab (2019), blocking interleukin (IL)-4 and IL-13 by targeting the α-unit of the shared IL-4 receptor. Data from phase III trials and real-world registries show favourable outcomes [7-11].

Reported treatment emergent adverse events from dupilumab are mostly mild and well-tolerable; injection site erythema, conjunctivitis and arthralgia are among the most reported. Furthermore, increased blood eosinophil count (BEC) is a common adverse event in patients under dupilumab therapy. This is true for CRSwNP patients, but also for those with asthma or atopic dermatitis treated with dupilumab [12-13]. Hypereosinophilia has generally been defined as a peripheral BEC greater than $1.5x10^9$ cells/L, which can be further divided into moderate ($1.5\text{-}5.0x10^9$ cells/L) and severe (>$5.0x10^9$ cells/L) [14]. A recent (non-systematic) review showed that hypereosinophilia occurs commonly in dupilumab-treated patients, regardless of their specific diagnosis/indication, and it regresses over time [15]. Drug-induced hypereosinophilia per se is not directly dangerous, but in case of dupilumab, some case reports and studies show that alongside the hypereosinophilia a hypereosinophilic syndrome (HES), eosinophilic vasculitis, or clinical manifestations of eosinophil-induced organ damage can arise [16-18]. This has led to the development of clinical protocols with strict monitoring of BEC under dupilumab treatment.

To the best of our knowledge, no studies exist that help define those patients at risk for hypereosinophilia and/or HES and/or associated organ damage. In the absence of such studies, it is possible that strict clinical protocols lead to increased health care utility without specifically targeting those at risk for HES. We therefore set out to investigate the prevalence of hypereosinophilia and HES in our dupilumab-treated cohort of CRSwNP patients, with special emphasis on the baseline BEC as a possible predictor of treatment-emergent hypereosinophilia.

Materials and methods

Our findings are reported from a real-life, prospective observational cohort treated with dupilumab. Eligible patients were adult (≥ 18 years) with severe CRSwNP with an indication for biological treatment per the EPOS2020 biological criteria and who started dupilumab as their primary biological add-on treatment [1]. The data from this cohort is collected in PolyREG, a multicentre registry for CRSwNP patients on biologicals in the Netherlands [8,11]. It currently holds data from the Amsterdam UMC, Alrijne Hospital (Leiden) and Isala Hospital (Zwolle; latter two teaching hospitals). On April 1st, 2023, all PolyREG patients treated with dupilumab and not with another biological before ("bio-naïve") were selected. Baseline measurements affected by recent (≤ 4 weeks) oral corticosteroids (OCS) use were discarded.

First, a cross-sectional analysis on all selected patients was carried out to evaluate the prevalence and course of dupilumab-induced hypereosinophilia by using BEC at baseline and during treatment up until and including 96 weeks of treatment (see measurement protocol below)
Secondly, patients with a treatment duration of at least 1 year, a reported baseline BEC and at least 2 of the 3 standardized follow-up measurements of BEC in the first 6 months were selected for further analysis. To help define those patients at risk for hypereosinophilia, baseline BEC values of patient groups who developed BEC ≥ $1.5x10^9$ cells/L and ≥ $3.0x10^9$ cells/L were compared. Furthermore, clinical characteristics and therapeutic consequences for patients with BEC ≥ $3.0x10^9$ cells/L were described. Baseline characteristics that were collected included age at start of therapy, gender, asthma (defined as regularly using inhaled corticosteroids as per the EPOS2020 biological criteria [1]), presence of non-steroidal anti-inflammatory drugs (NSAID)-exacerbated respiratory disease (N-ERD; defined as in the EEACI position paper on the diagnosis and management of N-ERD [19]), bilateral nasal polyp score (0-4 per side, 0-8 in total), and 22-item SinoNasal Outcome Test (SNOT-22) score.

Baseline and follow-up measurements of BEC were obtained according to a standardized protocol: at start, after four weeks of treatment, and every 12 weeks from baseline onwards. In case BEC was ≥ $1.5x10^9$ cells/L, the BEC was repeated every two weeks until it was again below $1.5x10^9$ cells/L. If patients (meanwhile) showed any signs or symptoms of HES, interim outpatient clinical check-ups were carried out including laboratory testing on serum eosinophil levels, adjoined by supplementary diagnostic testing as required. If BEC was ≥ $3.0x10^9$ cells/L, administration of dupilumab would be halted and patients monitored every two weeks until BEC was again below $1.5x10^9$ cells/L. In case of severe signs or symptoms likely attributable to or confirmed as HES, dupilumab treatment was immediately ceased. If despite halting dupilumab administration BEC remained high, patients would be prescribed a short course of OCS (typically 30 mg of prednisolone daily for 10 days). A switch to a different biological agent could be considered in case of persistent hypereosinophilia requiring multiple OCS courses and/or hampering regular treatment with dupilumab.
Data were obtained up until and including 96 weeks of treatment. During this period, dupilumab was auto-administered subcutaneously, 300mg once per two weeks (Q2W). Stepwise interdose interval prolongation by 2 weeks – as reported previously – ensued in those with moderate to excellent response, with minimal 24-week interim periods [8,11].

Statistical analysis

Statistical analyses were performed using Stata Statistical Software: Release 17. Normal distribution was tested using the Shapiro–Wilk test. Because not all groups were normally distributed non-parametric testing was performed. The Kruskal-Wallis test and Mann-Whitney U test were used for group wise comparisons. Data are presented as medians with interquartile range (IQR), unless otherwise specified. Baseline proportion characteristics (gender, asthma, N-ERD) were tested with a Fisher's exact test. BEC is expressed as number x 10^9 cells/L, which is not repeated elsewhere for purposes of readability. A Receiver Operating Characteristic (ROC) curve analysis and Area Under the Curve (AUC) with sensitivity and 1-specificity were calculated for BEC ≥ 3.0 during dupilumab treatment based on the baseline BEC.

Results

Altogether, 334 bio-naïve dupilumab-treated patients were included for cross-sectional analysis. At baseline, 3.8% of patients had BEC ≥ 1.5, and 0.3% had BEC ≥ 3.0 (Figure 1). Dupilumab-induced hypereosinophilia developed in a minority of patients, with a peak at week 12 (16.2% with BEC ≥ 1.5, and 1.7% ≥ 3.0, respectively). Selecting patients with a full dataset of BEC counts up until 96 weeks of treatment (n=86) did not relevantly alter the ratio between those with and those without hypereosinophilia per timepoint (data not shown).

In total, 218 patients had a treatment duration of at least 1 year and a reported baseline BEC. Their baseline characteristics are reported per patient group (developing BEC <1.5, BEC between ≥ 1.5 and < 3.0 and BEC ≥ 3.0 during treatment) in Table 1. There was a significant difference in baseline BEC values between patient groups (p<0.05).
Hypereosinophilia (BEC ≥ 1.5) manifested in 63 patients (28.9%), of whom 53 (24.3%) developed a BEC ≥ 1.5 and < 3.0. Their baseline BEC was 0.72 (0.58-1.01) and significantly higher than the baseline BEC of those not developing hypereosinophilia (0.42 (0.31-0.58), n=155, p<0.05). None of these 53 patients had a treatment deviation. Of the 218 patients, ten (4.6%) developed a BEC ≥ 3.0; their baseline BEC was also significantly higher than the baseline BEC of those not developing hypereosinophilia (1.12 (0.72-1.63) versus 0.42 (0.31-0.58); p<0.05) and of those developing BEC ≥ 1.5 and < 3.0 (1.12 (0.72-1.63) versus 0.72 (0.58-1.01); p<0.05). Baseline BEC for the full group ranged from 0.06 to 2.67. The lowest baseline value in the group developing BEC ≥ 1.5 was 0.21 and 0.55 for BEC ≥ 3.0. In other words, patients with a baseline BEC below 0.55 never developed a BEC ≥3.

In the full dataset (n=334), one more patient developed a BEC ≥ 3.0, but had a missing baseline value. As such, eleven patients were identified with a BEC of ≥ 3.0 in their follow-up of at least 1 year. The data and clinical development of these patients are listed in Table 2. None of these patients exhibited any other signs or symptoms of a hypereosinophilic syndrome. Four patients (4/11) developed BEC ≥ 3.0 during the protocolled extra measurements every two weeks following BEC ≥ 1.5.
Two patients switched to mepolizumab and are well controlled, the others could continue their dupilumab treatment and are now all well controlled (except for one patient who temporarily stopped treatment because of pregnancy).

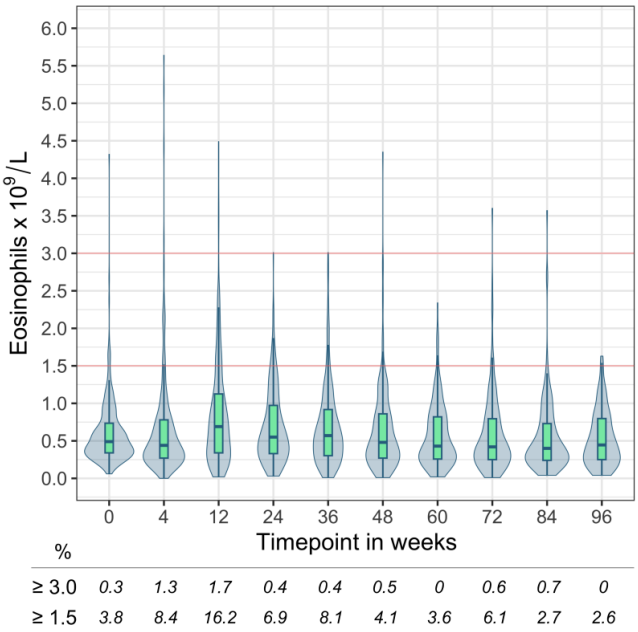

Figure 1. Blood eosinophil count during dupilumab treatment. Blood eosinophil count during treatment with dupilumab for severe uncontrolled chronic rhinosinusitis with nasal polyps in a real-world prospective observational multi-centre cohort, with the percentage of patients having eosinophils ≥ 1.5 and ≥ 3.0 in the table below per timepoint.

The optimal positive predictive value for baseline BEC was 1.52 with 37.5% developing BEC ≥ 3.0. The ROC analysis showed an optimal cut-off for baseline BEC at 0.96 to predict BEC ≥ 3.0 during dupilumab treatment, with an AUC of 0.79, a sensitivity of 0.70, a specificity of 0.84, a negative predictive value of 0.98 and a positive predictive value of 0.22.
No other baseline characteristics (e.g. asthma, N-ERD, or bilateral nasal polyp score) listed in Table 1 were predictive for developing hypereosinophilia or BEC ≥ 3.0.

Discussion

Our real-world cohort shows, transient hypereosinophilia (BEC levels ≥ 1.5) to be rather common in dupilumab-treated patients (28.9%). However, BEC levels ≥ 3.0 are relatively rare (4.6% of cases) and occur mainly in the first months of treatment. High baseline BEC levels are linked to treatment-emergent hype-

Table 1. Baseline demographics and clinical characteristics of patients with a follow-up of 1 year after dupilumab initiation.

	BEC ≤ 1.5 N=155	BEC ≥ 1.5 and < 3.0 N=53	BEC ≥ 3.0 N=11*	P-value
Age at start of therapy (year)	54 (43.5-61)	49 (37-60)	40 (30-57)	0.11
Gender (at birth)				0.94
Male	63.8%	62.3%	63.6%	
Female	36.2%	37.7%	36.4%	
Asthma	78.6%	86.8%	90.9%	0.38
N-ERD	34.0%	44.7%	45.5%	0.33
Bilateral nasal polyp score (0-8)	6 (5-6)	6 (6-6)	6 (4-7)	0.19
SNOT-22 score (0-110)	52 (41-64.5)	54.5 (43.5-67.5)	52.5 (44-69)	0.55
Baseline BEC	0.42 (0.31-0.58)	0.72 (0.58-1.01)	1.12 (0.72-1.63)	<0.05

Values are reported as: Median (interquartile range). * One patient was added to the BEC ≥ 3.0 group with an unknown baseline BEC value. Abbreviations: N-ERD: Non-Steroidal Anti-Inflammatory Drugs Exacerbated Disease. SNOT-22: 22-item SinoNasal Outcome Test. BEC: blood eosinophil count expressed as number $x10^9$ cells/L.

Table 2. Clinical characteristics of patients with blood eosinophil counts ≥ $3.0x10^9$ cells/L during dupilumab treatment.

Gender (at birth)	Age at start of therapy (years)	Baseline BEC	Highest BEC^	Therapeutic consequences	Outcome
Female	57	0.55	3.72	Missed dose: 2 OCS: 0	Well-controlled on dupilumab Q6W
Male	42	0.66	5.64	Missed dose: 5 OCS: 3	Switch to mepoluzimab and well-controlled
Male	38	0.72	3.31	Missed dose: 0 OCS: 0	Well-controlled on dupilumab Q6W
Male	59	0.96	4.42	Missed dose: 2 OCS: 0	Well-controlled on dupilumab Q6W
Male	24	1.09	3.31	Missed dose: 5 OCS: 0	Well-controlled on dupilumab Q6W
Female	29	1.15	3.50	Missed dose: 3 OCS: 0	Well-controlled on dupilumab Q6W
Male	42	1.37	4.39	Missed dose: 6 OCS: 1	Well-controlled on dupilumab Q2W
Male	33	1.63	5.72	Missed dose: 3 OCS: 0	Well-controlled on dupilumab Q6W
Female	29	1.68	8.61	Missed dose: 4 OCS: 2	Temporary stop because of pregnancy
Male	56	2.38	5.19	Missed dose: 2 OCS: 1	Well-controlled on dupilumab Q8W
Female	65	n/a	4.49	Missed dose: 2 OCS: 1	Switch to mepoluzimab and well-controlled

Abbreviations: QxW: treatment with dupilumab 300mg every x weeks. OCS: oral corticosteroids. BEC: blood eosinophil count expressed as number $x10^9$ cells/L. ^either from regular per protocol measurements or from extra in-between measurements.

reosinophilia with an optimal cut-off point of 0.96 to predict developing BEC ≥ 3.0. With a cut-off point of 0.55, patients never developed BEC ≥ 3.0. In the majority of patients, hypereosinophilia did not lead to therapeutic consequences and in no patients did it constitute or lead to HES or manifesting organ damage otherwise.

Hypereosinophilia has given rise to increased medical attention, additional blood tests, and sometimes extra treatment with systemic corticosteroids. Two cases in this cohort switched to another biological, mainly based on our prudence regarding high BEC levels, but not based on clinical signs/symptoms of eosinophil-induced organ damage.

On the one hand, one might therefore argue that this drug-induced hypereosinophilia is rare and clinically irrelevant; this would mean that strict BEC monitoring is not needed at all. On the other hand, one could also reason that eosinophil-induced adverse events are very rare and that the current data set is too small to completely ignore elevated BEC in dupilumab-treated patients. Furthermore, patients with BEC levels ≥ 3.0 experienced therapeutic consequences which could have prevented signs or symptoms of hypereosinophilic syndrome from developing. Eosinophilic conditions have been reported in patients treated with dupilumab but are relatively rare [16-18,20]. Extra monitoring and evaluation are generally appropriate in cases in which elevated eosinophil counts persist or when there are

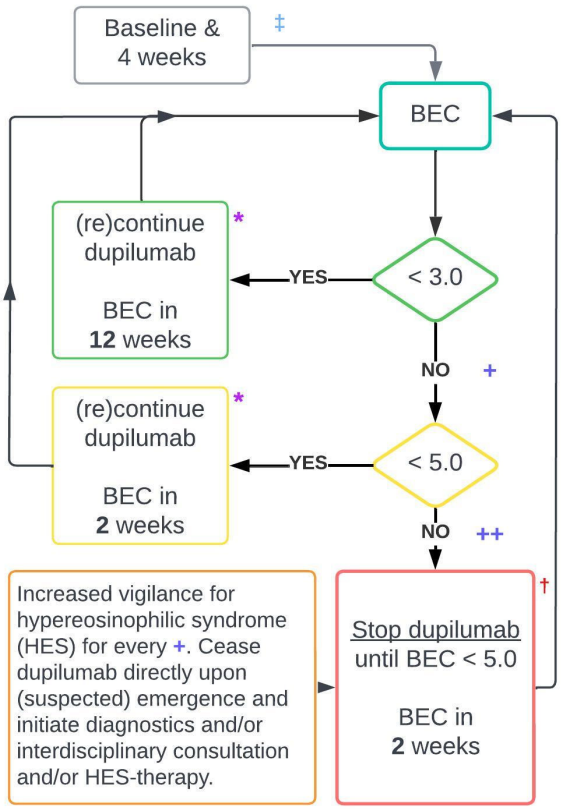

Figure 2. Clinical protocol for the detection and clinical decision-making in treatment-emergent hypereosinophilia during dupilumab therapy for chronic rhinosinusitis with nasal polyps. BEC: blood eosinophil count expressed as number x10^9 cells/L. * If prior BEC ≥ 5.0, consider increased dosing interval when re-initiating dupilumab. † Consider a short course of oral corticosteroids (OCS). In case of persistent (severe) hypereosinophilia consider switching to a different biological. ‡ Baseline BEC value ≥ 1.0 is a reason for increased clinical awareness.

signs or symptoms associated with a clinical suspicion for an eosinophilic condition, such as HES or eosinophilic granulomatosis with polyangiitis (EGPA). Factors such as maintenance therapy with OCS, the presence of antineutrophil cytoplasmic antibodies or neuropathy warrant extra vigilance for a potential EGPA [20].

From a 'principle of prudence' we propose that a BEC ≥ 3.0 should still be a reason for increased clinical awareness and follow-up. As patients reaching such levels already have relatively high BECs at baseline, a high baseline BEC justifies extra caution and close clinical monitoring. Precluding dupilumab use in these patients is not justified in our view, because even at the optimal predictive value of a baseline BEC of 1.52, ~60% of patients did not develop a BEC ≥ 3.0 in our dataset.

Based on these data, we have changed our local protocol (Figure 2). Baseline BEC values ≥ 1.0 are a reason for increased clinical awareness and counseling of the patient. Follow-up BEC values in dupilumab treated patients are obtained in the first year of treatment after 4 weeks and then every 12 weeks from treatment initiation. Only when BEC is ≥ 3.0, extra measurements every two weeks are performed and patients are monitored actively for signs/symptoms of HES. Only when BEC is ≥ 5.0, dupilumab administration is halted until BEC is <5, and/or oral corticosteroids are prescribed, which is largely in line with other proposals in literature [12]. Thus, the previous extra monitoring of patients with BEC ≥ 1.5 and <3.0 is now abandoned.

The main strength of this study is that the findings are reported from a large prospective observational cohort with standardized and structured indication criteria, treatment regimen and follow-up schedule.
However, some limitations remain. We state that hypereosinophilia did not lead to hypereosinophilia-related organ damage based on patients not experiencing any symptoms or signs. No screening assessment for organ-damage, such as echocardiogram, chest X-ray or neurologic evaluation was performed to rule out HES with certainty given the absence of any relevant complaints in our patient group. Furthermore, our propensity towards stepwise interdose interval prolongation might have dampened possible treatment-emergent hypereosinophilia after six months of follow-up as this is the time-point for the first prolongation. However, as the peak rise in BEC occurs already at 12 weeks of treatment, it seems unlikely that patients would develop relevant hypereosinophilia after six months of treatment when staying at the normal dosing of Q2W.

Conclusion

This study shows that BEC ≥ 1.5 usually abates with no therapeutic interventions and BEC ≥ 3.0 is rare. Hypereosinophilic syndrome did not occur and switching to a different biological on the count of persisting and/or severe hypereosinophilia is rarely needed.

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Authorship contribution

PK & RL: writing – original draft; data curation; formal analysis; visualization. JO, GA, LB, MC, DH, BR, VV: resources; writing – review & editing. SR & WF: conceptualization; methodology; resources; supervision; writing – review & editing.

Conflict of interest

RL has acted as a consultant and/or advisory board member for GSK. MC has acted as a consultant and/or advisory board member for Sanofi, ALK, Mylan, and Medtronic. BR has acted as

a consultant and/or advisory board member for Sanofi. VV has acted as a consultant and/or advisory board member for GSK. WJF has acted as a consultant and/or advisory board member and/or gave lectures for Sanofi, GSK, and Dianosic. SR has acted as a consultant and/or advisory board member for Sanofi, GSK, and Novartis. PK, JO, GA, LB, and RH have no (further) conflict of interest to disclose.

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Ethics

The study conformed to the Declaration of Helsinki. All patients consented to data collection and use in line with the GDPR. Approval of the institutional Medical Ethical Review Committee was granted for the PolyREG registry.

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