# Eosinophils are the dominant type2 marker for the current indication of biological treatment in severe uncontrolled chronic rhinosinusitis with nasal polyps*

Rik J.L. van der Lans[1], Josje J. Otten[1], Gwijde F.J.P.M. Adriaensen[1], Linda B.L. Benoist[1], Marjolein E. Cornet[2], D. Rienk Hoven[1], Albert B. Rinia[3], Wytske J. Fokkens[1], Sietze Reitsma[1]

[1] Amsterdam Rhinology Team (ART), department of otorhinolaryngology and head/neck surgery, Amsterdam University Medical Centers, location AMC, Amsterdam, The Netherlands

[2] Department of otorhinolaryngology, Alrijne Hospital, Leiden, The Netherlands

[3] Department of otorhinolaryngology, Isala Hospital, Zwolle, The Netherlands

**Rhinology 62: 3,** 383- 384, 2024
https://doi.org/10.4193/Rhin23.081

***Received for publication:**
February 23, 2023
**Accepted:** December 20, 2023

**Assocociate Editor:** Claire Hopkins

**Dear Editor:**

The latest European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS2020) defines markers for type2 inflammation in the context of indicating biological therapy in severe uncontrolled chronic rhinosinusitis with nasal polyps (CRSwNP) as either a total serum immunoglobulin E (total-IgE) >100 kU/L, a blood eosinophil count (BEC, expressed as $\cdot 10^9$ cells / L) ≥0.25, or a tissue eosinophil count ≥10 per high power field (HPF) [(1)]. Recently, an EPOS/EUFOREA expert panel advised to lower the threshold for BEC from ≥0.25 (EPOS2020) to ≥0.15 (EUFOREA2023) to align with thresholds used for biological indication in asthma patients [(2)]. As far as we know, there is no literature supporting the cut-off value for total-IgE.

PolyREG is a multicentre registry for CRSwNP patients on biologicals in the Netherlands [(3)]. The study population (n=300; details in the supplementary material) had a mean ± standard deviation BEC of 0.59 ± 0.39 and a total-IgE of 278 ± 514 kU/L at baseline. Table 1 shows these measurements in relation to EPOS2020 and EUFOREA2023 thresholds. In 89.3% of cases, BEC was sufficient to identify type2 inflammation by blood sampling according to EPOS2020.

There were 16 cases (5.3%) reaching the EPOS2020 type2 criterion solely based on total-IgE. Of these, 9 had BEC of ≥0.15. Of the remaining seven, four had a BEC within 3 months prior to baseline of ≥0.15 (of which three ≥0.25). For the other three patients, no earlier measurements were available.

In 16 cases (5.3%) neither the BEC nor the IgE cut-off according to EPOS2020 was reached; four of these cases though had tissue eosinophils ≥10 per HPF. Of the 16 cases, 12 met the EUFOREA2023 eosinophil threshold (of which two had tissue eosinophils ≥10 per HPF). Two of the remaining four cases also had tissue eosinophils ≥10 per HPF. For the remaining two cases no earlier measurements of BEC or tissue eosinophil counts were available. As such, these two did not comply with the EPOS2020 or EUFOREA2023 type2 criterion at baseline; one stopped therapy for being a non-responder, the other is clinically controlled on dupilumab.

Thus, when applying the EUFOREA2023 eosinophil threshold, type2 inflammation was established in 96.3% of cases based on BEC alone. Using tissue eosinophils or repeated measurements of BEC would raise this number to at least 98.3%. Conversely, in 43.3% of patients with an indication for biological therapy, total-IgE was <100 kU/L.

Limitations of our current data: 1) this is a Dutch cohort and possibly, findings might be different in other countries; 2) possible selection bias, i.e., only patients with an indication according to EPOS2020 were included. Apparently, the other inclusion criteria already predispose to a selection of patients were BEC ≥ 0.15 is highly likely and non-discriminative. From the paucity of clinically readily available biomarkers, only total-IgE can be used as a discriminator in this highly selective patient group.

Still, elevated total-IgE is an ambiguous marker between diseases such as allergic rhinitis (monoclonal IgE) and CRSwNP (polyclonal IgE) or other allergic conditions. Moreover, there are no clear cut-offs to distinguish them. From our data, it is clear that BEC is the main determinant of the type2 criterion for the indication of biological treatment. In case of doubt about a type2 inflammatory endotype, we would advise at least repeating BEC (or use tissue eosinophils). Still, a total-IgE is needed in a minority of patients (depending on cut-off: 1.7% - 5.3%) to meet

Table 1. Baseline measurements of 300 CRSwNP patients indicated for biological therapy in relation to the EPOS2020 and EUFOREA2023 thresholds.

| Criteria<br>EPOS2020 | Total-IgE ≥ 100 | Total-IgE < 100 | Total |
|---|---|---|---|
| BEC ≥0.25 | 154 (51.3%) | 114 (38.0%) | 268 (89.3%) |
| BEC <0.25 | 16 (5.3%) | 16 (5.3%) | 32 (10.7%) |
| Total | 170 (56.7%) | 130 (43.3%) | 300 (100%) |
| **EUFOREA2023** | **Total-IgE ≥ 100** | **Total-IgE < 100** | **Total** |
| BEC ≥0.15 | 163 (54.3%) | 126 (42.0%) | 289 (96.3%) |
| BEC <0.15 | 7 (2.3%)^ | 4 (1.3%)§ | 11 (3.7%) |
| Total | 170 (56.7%) | 130 (43.3%) | 300 (100%) |

BEC: blood eosinophil count · $10^9$ cells / L; Total-IgE: total serum immunoglobulin E in kU/L; ^ of these, 4 had a measurement of blood eosinophils within three months prior to baseline above threshold; § of these, 2 had tissue eosinophils ≥10/high power field.

the type2 criterion, and when considering omalizumab therapy (between 30 and 1500 kU/L to establish treatment dosage). Whether the discrimination based on total-IgE < or ≥100 kU/L is clinically relevant (e.g., for outcomes) remains to be elucidated.

## Authorship contribution

RvdL, JO, GA, LB, MC, RH, BR, SR collected the data; RvdL and SR analysed the data; WF and SR wrote the manuscript; All authors gave their input for the final version of the manuscript.


## Funding

There was no funding of this work.


## 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.
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. The department of otorhinolaryngology and head/neck surgery of the Amsterdam UMC has received research funding from Sanofi, GSK, and Novartis. The department of oto-rhinolaryngology of the Alrijne Hospital has received research funding from GSK. JO, GA, LB, and RH have no (further) conflict of interest to disclose.

## References


1. Fokkens WJ, Lund VJ, Hopkins C, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. Rhinology. 2020 Feb 20;58(Suppl S29):1-464.
2. Fokkens WJ, Viskens AS, Backer V, et al. EPOS/EUFOREA update on indication and evaluation of Biologics in Chronic Rhinosinusitis with Nasal Polyps 2023. Rhinology. Rhinology. 2023 Jun 1;61(3):194-202.
3. van der Lans RJL, Fokkens WJ, Adriaensen GFJPM, et al. Real-life observational cohort verifies high efficacy of dupilumab for chronic rhinosinusitis with nasal polyps. Allergy. 2022 Feb;77(2):670-674.



Sietze Reitsma
Department of otorhinolaryngology and head/neck surgery
Amsterdam University Medical Centers,
location AMC
Meibergdreef 9
1105 AZ Amsterdam
the Netherlands

E-mail: s.reitsma@amsterdamumc.nl


**This manuscript contains online supplementary material**

## SUPPLEMENTARY MATERIAL

### Patient selection

PolyREG is a multicentre registry for CRSwNP patients on biologicals in the Netherlands. It currently holds data from the Amsterdam UMC and from Alrijne Hospital (Leiden), and Isala Hospital (Zwolle; latter two teaching hospitals). On December 1st, 2022, all PolyREG patients not treated with another biological before ("bio-naive"), with both BEC and total-IgE available at baseline were selected (n=307). Seven were excluded, because their baseline samples were collected during or shortly (4-6 weeks) after treatment with systemic corticosteroids. The baseline measurements were used to analyse the type2 criterion for the indication of biologicals and were retrieved before any choice for biological (omalizumab, mepolizumab, or dupilumab) was made.