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RESEARCH ARTICLE

Single-center off-label benralizumab use for refractory hypereosinophilic syndrome demonstrates satisfactory safety and efficacy

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Abstract

Introduction: Benralizumab is an interleukin 5-receptor-blocking drug registered for the treatment of eosinophilic asthma. It has proven efficient and safe in a small phase-II trial in hypereosinophilic syndrome and is currently being investigated in a larger, randomized phase-III trial. We report on real-world experience with benralizumab in 15 patients with severe Hypereosinophilic syndrome (HES) that were refractory to other treatments or on unacceptable steroid doses.

Methods: Fifteen patients with severe HES were treated with compassionate need benralizumab. The measured endpoints were a reduction in peripheral eosinophil count, a reduction of corticosteroid use, adverse events, and clinical response.

Results: All subgroups of HES were represented in this cohort and in the case of reactive HES, treatment of the primary cause did not lead to resolution of the eosinophilia. The median time of follow-up was 38 months. Twelve patients reached a normalized peripheral eosinophil count ($< 0.05 \times 109/L$), while the remaining three patients also had a significant reduction from baseline.

Of the eight patients initially treated with steroids, five patients were off steroids completely, and three patients had reduced dosages. Eight patients experienced complete symptom resolution, and five partial resolution. No serious adverse events were observed.

Conclusion: In conclusion, benralizumab is safe and effective for the treatment of HES.

KEYWORDS
antibody therapy, eosinophils, granulocytes

1 | INTRODUCTION HYPEREOSINOPHILIC SYNDROME (BENRALIZUMAB)

Hypereosinophilic syndrome (HES) encompasses a rare, heterogeneous group of disorders defined by persistently elevated absolute eosinophil count in peripheral blood (> 1.5×10^9/L) or tissue, manifestations of associated end-organ damage attributable to hypereosinophilia and absence of other explanations for organ damage [1, 2].

HES is conceptually split into four main categories: primary (neoplastic/clonal hematopoiesis, HE_n), secondary (reactive, due to eosinophilic stimulating cytokines, R-HES) familial (HE_{FA}), and HE of undetermined significance (HE_{us}) [3].

A careful diagnostic work-up, as well as vigilant surveillance for end-organ damage, should be performed to establish an appropriate diagnosis and to treat or prevent end-organ damage [4]. Untreated or inadequately controlled HES confers a risk of irreversible damage and even mortality, for instance in the case of cardiac involvement [5].

Treatment depends on etiology and may consist of corticosteroids, and tyrosine kinase inhibitors such as imatinib mesylate, hydroxycarbamide, interferon-alpha, or mepolizumab, with varying responses. Corticosteroids have historically been the cornerstone of HES therapy, but are not always effective. The efficacy of corticosteroids also varies with the subtype of HES [6]. Furthermore, long-term use results in negative outcomes, including osteoporosis, diabetes mellitus, and decreased immunity. Attempts to treat HES patients with steroid-sparing agents are often unsuccessful due to ineffectiveness or medication intolerance [7]. The shortcomings of glucocorticoids and cytoreductive agents have therefore highlighted a need for alternative treatments.

More aggressive treatments, such as alemtuzumab, are effective for the reduction of eosinophils, but are severely immunosuppressive, with frequent relapses after discontinuation, infusion reactions, and secondary auto-immune disease or infection [8, 9]. Mepolizumab, which is a neutralizing anti-interleukin 5 (anti-IL5) antibody, was demonstrated to be effective in reducing HES flares and peripheral eosinophil count in a randomized phase-III trial and is the only IL5 blocking agent currently registered for the treatment of HES [10].

Benraluzimab is a humanized afucosylated anti-IL5 receptor alpha (anti-IL5R alpha) monoclonal antibody that directly targets eosinophils. Benralizumab depletes eosinophils in the peripheral blood and mucus in patients with asthma and is currently registered by the US Food and Drug Administration and European Medicines Agency for the treatment of severe eosinophilic asthma [11, 12]. A phase II trial has shown that benralizumab is effective in *PDGFRA*-negative HES [13] A randomized, placebo-controlled, phase III trial for the treatment of HES with benralizumab is currently ongoing (NATRON, NCT04191304).

We report on the off-label use of benralizumab in 15 patients with HES that were either refractory to conventional therapy or were on unacceptably high corticosteroid doses. This observatory, single-center patient series displays a real-world experience of benralizumab use in clinical practice.

TABLE 1 Patient characteristics.

Variable	Data
Number of patients	15
Sex (m:f)	10:5
Median age at the start of treatment (range)	60 (31–69)
Type of HES	
L-HES	2 (13%)
i-HES	9 (60%)
R-HES	3 (20%)
HES_n*	1 (7%)
Steroid responsive	
Patients on steroids at the start of treatment	8 (53%)
Median steroid dosage (mg) at start of treatment (range)	20 (7.5–40)
Patients off of steroids at the end of treatment	6 (75%)
Patients previously treated with mepolizumab	3(20%)

Abbreviations: HES_n, neoplastic hypereosinophilic syndrome; i-HES, idiopathic hypereosinophilic syndrome; L-HES, lymphocytic hypereosinophilic syndrome; R-HES, reactive hypereosinophilic syndrome.

2 | METHODS

All 15 adults with various subsets of HES that started treatment with off-label benralizumab at our institution from 2019 to 2022 were included in this retrospective analysis. These patients either had refractory HES or were treated with unacceptably high doses of corticosteroids. After giving consent for off-label use the patients were treated with a benralizumab dose of 30 mg subcutaneously at a frequency of every 4 weeks. All patients received the first two doses on an outpatient basis in a daycare unit. Subsequent doses were self-administered at home. Dosing frequency was adjusted to every 6 or 8 weeks depending on the treatment response per individual patient (Table 1).

Patients were followed every 4–12 weeks by their treating physician with clinical history, physical examination, and laboratory measurements of full blood count, including differential, liver enzymes, and kidney function. Other follow-up parameters were determined by the type of organ involvement at the initial presentation.

The primary endpoint of this analysis was a reduction of eosinophils in the peripheral blood below < 0.6×10^9/L. Secondary endpoints included: reduction of corticosteroid use, adverse events, and clinical response. Information regarding organ function and clinical response was collected from patient files, including subjective accounts of symptom reduction. Data was collected between July 2019 and November 2023. A distinction was made between complete remission (CR) and partial remission (PR), where the former refers to both a complete

resolution of peripheral eosinophilia and symptoms, and the latter refers to either [1] partial resolution of symptoms [2], resolution of eosinophilia with persisting symptoms, or [3] complete reduction of eosinophilia and symptoms while on ≥10 mg of prednisone or an equivalent per day.

3 | RESULTS

3.1 | Patient characteristics

Of the 15 patients included, 10 were male and five were female. The mean age of the patient population was 60 (range 31–69). The most common diagnostic subtype was i-HES (9, 60%); the rest of the subtypes were evenly distributed (2, 13%). All baseline- and disease characteristics of the patients can be found in Tables 1 and 2.

One patient (#15) was ultimately diagnosed with myodysplastic syndrome (MDS) despite the absence of this diagnosis in the bone marrow examination (morphology, flowcytometry, cytogenetics, and molecular MDS/acute myeloid leukemia panel) performed at the start of benralizumab treatment.

None of the included patients had a *FIP1L1/PDGFRA*- or *PCM1/JAK2* fusion gene or rearrangement of *PDGFRB* or *FGFR1*, as confirmed by HES FISH. Next-generation sequencing (NGS) was performed for 11 patients to exclude clonal hematopoiesis. The diagnosis of L-HES was assigned to patients who had abnormal T-cell phenotypes by flow cytometry. Patients with a clonal T-cell population by T-cell receptor gene re-arrangement analysis in the absence of an aberrant phenotype were excluded from the L-HES diagnosis.

In the patients with reactive HES, other than L-HES, treatment of the primary cause did not result in a decrease in eosinophils. One of these patients (patient #10) had underlying sarcoid disease. Other entities such as immunoglobulin 4 disease, or Hodgkin's- or non-Hodgkin's disease had been excluded upon repeat biopsies.

Patient #11 had a long history of intermittent HES flares without established etiology after multiple rounds of thorough diagnostic work-ups including splenectomy, multiple bonemarrow examinations, and positron-emission tomography scans. She was dependent on high doses of corticosteroids but had a CR after initiation of benralizumab without further need for corticosteroids. She developed lymphadenopathy 2 years later and after multiple biopsies was diagnosed with HHV8+ multicentric Castleman's disease (MCD) for which she was treated with chemo-immunotherapy and has remained in remission.

All included patients had elevated eosinophil counts above 0.6×10^9/L at the start of treatment, with the exception of one patient with a level of 0.32×10^9/L while on 30 mg prednisone per day. Three patients previously received mepolizumab treatment (300 mg subcutaneously), two of whom were refractory and subsequently stopped, while one had a supposed allergic reaction that was not witnessed by a physician but was deemed serious enough to stop further administration of the drug. The average follow-up time after starting benralizumab was 38 months, with a range of 17–50 months. Eight patients were on corticosteroids at the beginning of treatment, and three patients were receiving non-steroidal co-medication during the course of their treatment.

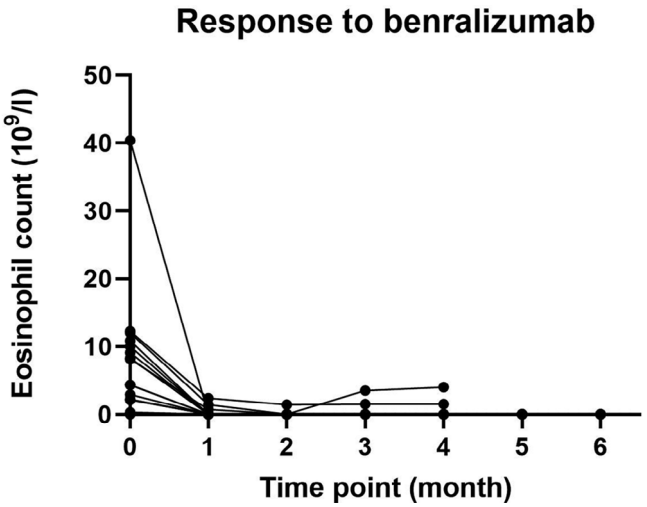

FIGURE 1 This figure demonstrates that 13 out of 15 patients experienced a reduction of peripheral eosinophils below 0.5 × 10^9/L.

3.2 | Efficacy

13 patients (86%) rapidly achieved a reduction in their peripheral eosinophil count to below 0.6×10^9/L, while patient #9 had a reduction from 8.13 to 0.72×10^9/L after the first administration, with a count eventually normalized while stopping all other medications (Figure 1) Of the eight patients receiving corticosteroids, all but two patients were able to stop them completely after 4 months. Eventually, all but one patient was able to completely stop corticosteroids (Figure 2). Ten patients experienced an improvement of symptoms, with eight patients reaching complete resolution of symptoms and signs. This includes two patients (patients #2 and #4) who displayed a normalization of cardiac parameters. More specifically, patient #2 had an improvement in heart failure status (NYHA III to I), with an improved left ventricular function as confirmed by echocardiogram, while patient #4 had an improved cardiac function confirmed by echocardiogram, and improved pulmonary function as assessed by spirometry and lung diffusion capacity. Three patients did not experience complete clinical improvement despite decreased peripheral eosinophilia; patients #3 and #12 had persisting colitis, and patient #8 had persisting skin involvement. Furthermore, two patients had an initial response to benralizumab, but had a relapse after 2 months, demonstrating both an increase in eosinophil counts as well a relapse of clinical symptoms. All patients with objective clinical benefit remain on treatment at the moment of writing of this manuscript.

With regards to subtype, both L-HES patients showed significant improvement in their disease, but patient #14 had an early relapse and was also unresponsive to alemtuzumab. The patients with i-HES

TABLE 2 Patient characteristics.

Patient	Age at the start of treatment	Sex	Diagnosis	Presentation/organ involvement	Reason for Benralizumab Treatment	Dose	Follow-up since the beginning of treatment (months)	Treatment duration if benralizumab was discontinued (months)	Benralizumab cessation (Yes/No, reason)	Eosinophil count at the time of beginning of Treatment *	Last recorded eosinophil count*	Toxicity	Co-medication	Effect on organ function	Response
Patient 1	37	M	i-HES	Pleural effusion, malaise, fatigue, jaundice, Dermatological abnormalities	Prednisone, hydrea, interferon, and imatinib ineffective; steroid-induced diabetes from prednisone	30 mg/8 wk	34	N.A.	No	Unknown	<0.05	None	None	Already been resolved with prednisone	CR
Patient 2	69	M	i-HES	Eosinophilic myocarditis	Hydrea ineffective, interferon intolerance	30 mg/6 wk (refractory at 8 wk)	34	N.A.	No	4.37	<0.05	Herpes zoster	None	NYHA class III → I	CR
Patient 3	45	F	i-HES	Urticaria, dyspnea, colitis	Mesalazine and azathioprine are ineffective, budesonide toxicity (colitis), contra-indication to hydrea	30 mg/6 wk	34	N.A.	No	2.24	<0.05	Headache	Azathioprine, budesonide	decreased urticarial, decreased dyspnea, persisting colitis	PR
Patient 4	62	M	i-HES	Perimyocarditis, asthma	Hydrea and imatinib are ineffective, and steroid dependency (cannot be titrated to < 40 mg)	30 mg/4 wk	20	12	Yes, ineffective (could not titrate prednisone down)	10.03	1.15	None	Prednisone, foster	Resolution of myocarditis and pulmonary function	PR, switch to mepolizumab with CR
Patient 5	39	F	i-HES	Ascites, abdominal pain	Interferon and hydrea ineffective, steroid dependency	30 mg/4 wk (refractory at 8 wk)	25	N.A.	No	10.85	<0.05	None	None	Resolution of ascites and abdominal pain	CR

(Continues)

TABLE 2 (Continued)

Patient	Age at the start of treatment	Sex	Diagnosis	Presentation/organ involvement	Reason for Benralizumab Treatment	Dose	Follow-up since the beginning of treatment (months)	Treatment duration if benral-izumab was discontin-ued (months)	Benralizumab cessation (Yes/No, reason)	Eosinophil count at the time of beginning of Treatment *	Last recorded eosinophil count*	Toxicity	Co-medication	Effect on organ function	Response
Patient 6	68	M	i-HES	Myocarditis, asthma	Hydrea toxicity (bone marrow dysplasia), interferon intolerance, steroid dependency	30 mg/ 8wk	22	N.A.	No	9.09	<0.05	Skin rash on feet and hands at the start of treatment	None	Resolution of all complaints	CR
Patient 7	65	M	i-HES	Urticaria, anaphylaxis, colitis	Hydrea ineffective, interferon intolerance, imatinib ineffective, steroid dependency	30 mg/ 8 wk	22	N.A.	No	2.95	<0.05	None	Vedolizumab	Resolution of all complaints	CR
Patient 8	68	F	i-HES	Skin rash, severe urticarial	Cyclosporine, anakinra, and mepolizumab ineffective; steroid dependency	30 mg/ 4 wk	6	N.A.	No	0.32	<0.05	None	None	Persistent dermatologi-cal symptoms	PR
Patient 9	31	M	i-HES	Hepatitis, stroke, retinal vein occlusion	Refractory under steroid, hydrea, imatinib, nilotinib, and mepolizumab use	30 mg/ 4 wk	2	N.A.	No	8.13	0.5	None	None	Resolution of all symptoms	CR
Patient 10	49	M	R-HES due to sarcoido-sis	Retrosternal pain, facial edema	Insufficient effect from budesonide, MTX; steroid dependency	30 mg/ 6 wk (refractory at 8 wk)	6	18	No	4.35	0.05	None	None	Resolution of all complaints	CR

(Continues)

TABLE 2 (Continued)

Patient	Age at the start of treatment	Sex	Diagnosis	Presentation/organ involvement	Reason for Benralizumab Treatment	Dose	Follow-up since the beginning of treatment (months)	Treatment duration if benralizumab was discontinued (months)	Benralizumab cessation (Yes/No, reason)	Eosinophil count at the time of beginning of Treatment *	Last recorded eosinophil count*	Toxicity	Co-medication	Effect on organ function	Response
Patient 11	35	F	R-HES	Ascites, abdominal pain	MTX and imatinib insufficient, steroid dependency	30 mg/4 wk	18	N.A.	No	40.4	<0.05	None	None	Persistent ascites (attributable to Castleman)	CR
Patient 12	19	M	R-HES due to IBD	Colitis, ascites	Mesalazine, adalimumab, azathioprine, vedolizumab, and MTX (for colitis) ineffective	30 mg/4 wk	34	4.5	Yes, ineffective	2.15	0.05	None	Budesonide	Steroids titrated down, persistent colitis	Unresponsive
Patient 13	60	F	L-HES	Fatigue, fever, cough	Hydrea ineffective, interferon intolerance, steroid dependency	30 mg/4 wk (refractory at 8 wk)	23	N.A.	No	8.3	<0.05	None	None	Resolution of all complaints	CR
Patient 14	64	M	L-HES	Myositis, edema	Imatinib and mepolizumab ineffective, interferon intolerance, steroid dependency	30 mg/4 wk	1	N.A.	No	12	1.12	None	None	Symptoms briefly responded	Unresponsive after a short initial response. Failed alemtuzumab.
Patient 15	58	M	HES_N, later MDS/MPN	Coughing	Prednisone and imatinib ineffective, thrombopenia due to hydrea	30 mg/4 wk	13	1.8	Yes, thrombopenia	12.26	1.45	Headache	None	80% less coughing	Responded partially on eosinophil count but died from MDS

*In units of 10^9/L.
**V617F mutation.
Abbreviations: CR, complete response; IBD, inflammatory bowel disease; i-HES, idiopathic hypereosinophilic syndrome; L-HES, lymphocytic hypereosinophilic syndrome; MDS, myodysplastic syndrome, MPN, myoproliferative neoplasm; MDS/MPN-u, unclassifiable myodysplastic syndrome/myoproliferative neoplasm; MTX, methotrexate; PR, partial response.

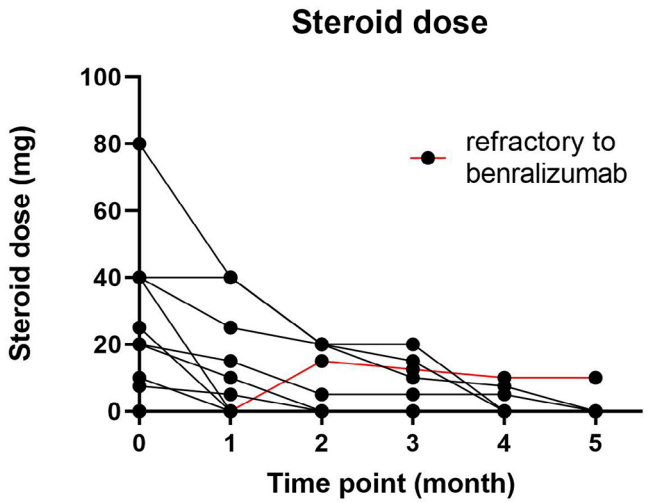

FIGURE 2 Effect of benralizumab on corticosteroid use. Within the first 4 months, all but two patients were able to stop corticosteroids completely. After 6 months, only one patient remained dependent on corticosteroids, due to refractory symptoms following benralizumab treatment.

had a more varied response. Of the nine i-HES patients, Five had a CR. Three patients (patients #3, #4, and #8) had a partial response. More specifically, while patient #4 had clinical improvement in cardiac function, the corticosteroid dose could not be titrated down due to a decrease in pulmonary function. He was eventually switched to mepolizumab with a CR as a result without corticosteroids. In contrast, patients #3 and #8 had normalized eosinophilia but unresolved symptomology. One (11%) patient (patient #12) was fully unresponsive to treatment; mepolizumab was also not effective in this patient. Of the three R-HES patients, two patients reached CR, while patient #12 had a PR with normalized peripheral eosinophilia yet persistent colitis.

3.3 | Safety

Benralizumab was well tolerated in this cohort. Patient #3 experienced a mild headache for a few days after the first dose, as did patient #15. Patient #6 had a mild malar rash after the first dose. All reactions were self-limiting. Patient #2 experienced a re-activation of the herpes zoster virus, which was subsequently treated with valaciclovir. This patient also went on to have a full clinical remission. No site or administration reactions, nor serious adverse events were observed within our cohort.

4 | DISCUSSION

In this retrospective real-world cohort study, we treated 15 patients with refractory or steroid-dependent HES with benralizumab. Twelve out of 15 (80%) of patients achieved peripheral eosinophil counts below 0.6×10^9, permitting full cessation of corticosteroids in seven out of the eight patients initially treated with steroids. This success rate is similar to that found by Kuang et al, with an efficacy rate of 74%, which was also reported to be similar to the efficacy of corticosteroids and mepolizumab [13]. Benralizumab was also well tolerated, which is in line with previous research, corroborating evidence that benralizumab is a safe drug to administer [13, 14].

It has been demonstrated previously that the HES subtype can be predictive of clinical response to biologicals and that L-HES patients are the least likely to respond to anti-IL5 therapy [15]. In our study, only one of the two L-HES patients had a significant and durable response, but these numbers are too small to make a comparison with other reports.

Several patients within our cohort had normalized eosinophil counts without clinical improvement. Such is the case for patient #12 with persistent colitis, which was likely more attributable to the inflammatory bowel disease (IBD) rather than HES. In fact, the lack of clinical response was ultimately the main motivation for the change of diagnosis in this patient from iHES to IBD. Patient #4 had clinically significant improvement but the colitis persisted. Likewise, patient #11 had persistent dermatological manifestations despite normalized peripheral eosinophil counts. No other diagnosis was found in the latter two patients. Because we have only measured peripheral eosinophils, we cannot rule out insufficient eosinophil depletion in tissue. This difference between efficacy in terms of eosinophil count and clinical response is, however, far from unique. The role of peripheral and tissue depletion of eosinophils in gastrointestinal eosinophilic disorders, for instance, remains unclear. Previous research suggests the lack of clinical improvement mostly occurs within the upper gastrointestinal tract, where there is more cell turnover in the epithelium [14, 16]. But this leaves the persistent colitis unexplained. And a recently published randomized phase-III trial with benralizumab in eosinophilic esophagitis demonstrated a clear discrepancy between clinical improvement and histological response. In this trial, histological response did not significantly reduce clinical symptoms [17].

Interestingly patient #4 did not respond to benralizumab but had an excellent response to mepolizumab. Patients #8 and #9 did not benefit from mepolizumab treatment but did respond to benralizumab, with the former patient reaching PR and the latter patient a CR. The effects of benralizumab and mepolizumab are mediated by different mechanisms. However, this difference is not reflected in clinical practice, given the similar rates of efficacy in eosinophilic disorders [18]. For our patients, we do not have sufficient data to explain this difference in response.

Limitations of this study include our small sample size, limiting our ability to carry out robust statistical subgroup analysis. Furthermore, eosinophils were measured in peripheral blood, but not tissues, giving us limited information regarding pathogenesis. It also limits our ability to explain the aforementioned discrepancy between a decreased eosinophil count and symptom resolution. Furthermore, due to the retrospective nature of this study, additional parameters were not included, including serum drug levels of benralizumab, serum antidrug-

antibody level, and serum IL-5 levels, amongst others. Furthermore, the retrospective nature entails that not all patients received the exact same diagnostics.

Despite these limitations, this retrospective real-world cohort study shows that benralizumab is a safe and effective treatment for patients with refractory HES. It is highly effective in reducing peripheral eosinophil count, improving clinical signs and symptoms, and reducing steroid use. Furthermore, in line with earlier research, our study shows that benralizumab is associated with few and mild side effects. Of note, some patients respond better to benralizumab than to mepolizumab and vice versa. Benralizumab therefore is a valuable addition to the available therapeutic options for HES. Further research with larger numbers of participants in randomized trials will be needed to further validate the effects of benralizumab, and to compare its therapeutic characteristics to other IL-5 targeting biologicals.

AUTHOR CONTRIBUTIONS

Yvonne Veltman performed a chart review and co-wrote the manuscript.

Anna M. Aalbers performed a chart review, co-wrote the manuscript, and made tables.

Maud A. W. Hermans co-initiated the research, took an active role in patient care, and co-supervised the manuscript.

Pim G. N. J. Mutsaers initiated the research, made figures and tables, co-wrote the manuscript, and supervised the project and final drafts of the research.

CONFLICT OF INTEREST STATEMENT

Pim G. N. J. Mutsaers has received research funding from Astra Zeneca outside the scope of this manuscript.

FUNDING INFORMATION

There was no funding provided for this study.

DATA AVAILABILITY STATEMENT

Since this is a retrospective analysis of patient data, these data cannot be accessed by anyone other than the authors.

ETHICS STATEMENT

No ethics approval has been requested since this was a retrospective study. No procedures or data management was performed outside routine clinical care.

PATIENT CONSENT STATEMENT

The data has been anonymized and no one other than their own clinicians has had access to the medical files. Therefore, no consent was necessary according to our local ethical guidelines.

CLINICAL TRIAL REGISTRATION

The authors have confirmed clinical trial registration is not needed for this submission.

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