



## LETTER

## Decreased concentrations of C5a complement receptor antibodies are associated with relapse in eosinophilic granulomatosis with polyangiitis (EGPA)

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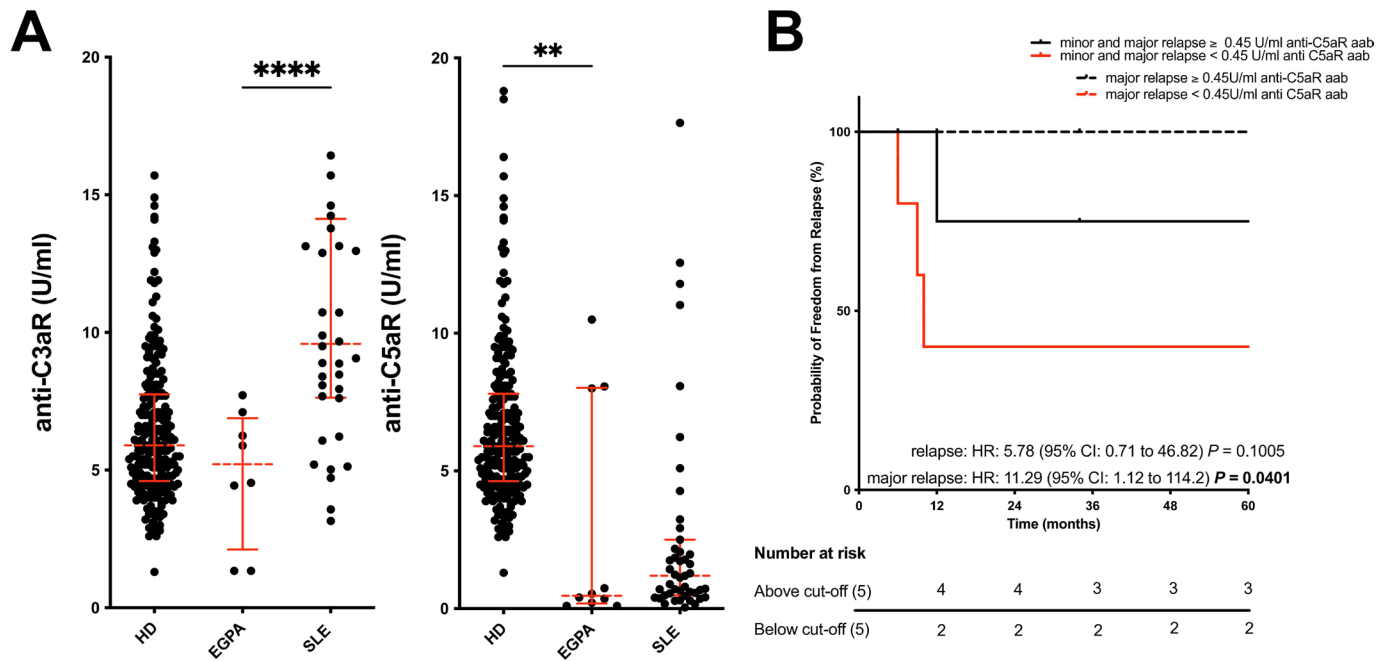
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Complement activation via the alternative pathway with subsequent generation of the C5a complement fragment has an important role in anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV) pathophysiology.<sup>1</sup> Binding of C5a to the G protein-coupled receptor (GPCR) C5a receptor 1 (C5aR1, CD88) boosts neutrophil activation and induces severe vessel necrosis in experimental myeloperoxidase-specific (MPO)-ANCA-induced glomerulonephritis.<sup>2</sup> Moreover, the glucocorticoid-sparing oral C5aR antagonist avacopan improves disease control and renal recovery in granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA), the two major subgroups of AAV.<sup>3</sup> Notably, serum concentrations of endogenous anti-GPCR antibodies targeting C3a and C5a complement receptors are decreased in GPA and MPA compared with healthy individuals. Lower concentrations of anti-C5aR antibodies, but not anti-C3aR antibodies, were associated with disease activity and relapse suggestive of C5aR as an immune checkpoint regulated by endogenous anti-C5aR antibodies in AAV.<sup>4</sup> Similar to neutrophils, eosinophils constitutively display C5aR1 expression.<sup>5</sup> As suggested by an earlier study showing increased C4 complement and CH50 serum concentrations, complement activation may also play a role in eosinophilic granulomatosis with polyangiitis (EGPA), the third and minor subgroup of AAV characterised by eosinophil-rich necrotising granulomatous inflammation and systemic small vessel vasculitis.<sup>6</sup> Therefore, we were

**Table 1** Demographic and clinical findings of enrolled subjects

Clinical characteristics	Patients with EGPA, n (%)
Patients	10*
General characteristics	
Age in years, median (range)	61 (28–78)
Sex, women/men	8/2
New/relapsing/remission	7/2/1
BVAS V3.0†, median (range)	10.5 (0–19)
Clinical manifestations, n (%)	
Ear, nose, throat	8 (80)
Pulmonary	3 (30)
Renal	3 (30)
Cardiovascular	7 (70)
Gastrointestinal	5 (50)
Cutaneous	2 (20)
Nervous system	3 (30)
Serological findings	
MPO ANCA‡	1 (10)
hs-CRP, mg/L (mean±SD)	38.16±64.67
Creatinine, µmol/LI (mean±SD)	122.40±98.79
Eosinophil count at time of diagnosis in/µL, mean, (range)	5880 (620–22000)
Eosinophil count at the time of study inclusion in/µL, mean, (range)	2178 (550–11470)
Treatment, n (%)	
Cyclophosphamide	2 (20)
Azathioprine	1 (10)
Glucocorticoid	5 (50)
Glucocorticoid dose, median (range)	10.5 (5–30)

\*All patients fulfilled the 2022 ACR/EULAR Classification Criteria for Eosinophilic Granulomatosis with Polyangiitis.  
†Birmingham Vasculitis Activity Score version 3.  
‡Myeloperoxidase-specific ANCA (antineutrophil cytoplasmic autoantibody). ANCA, anti-neutrophil cytoplasmic autoantibody; BVAS, Birmingham Vasculitis Activity Score; EGPA, eosinophilic granulomatosis with polyangiitis; hs-CRP, high-sensitivity C-reactive protein; MPO, myeloperoxidase.



**Figure 1** (A) In contrast to anti-C3aR, anti-C5aR aab levels were decreased in EGPA compared with healthy donors (median with IQR; one-way analysis of variance with Tukey's multiple comparison post hoc test). (B) Patients with anti-C5aR levels below 0.45 U/mL displayed an increased individual risk for major relapse within 12 months (Kaplan-Meier survival curves, HR: 11.29, 95% CI: 1.12 to 114.2,  $p=0.0401$ ). Aab, autoantibodies; EGPA, eosinophilic granulomatosis with polyangiitis; HD, healthy donors; SLE, systemic lupus erythematosus. \*\*\*\*  $p<0.0001$ , \*\*  $p<0.01$ .

interested in examining anti-C3aR and anti-C5aR antibody concentrations and analysing their association with disease activity and relapse in EGPA.

Serum anti-C3aR and anti-C5aR antibodies were detected using commercially available solid-phase sandwich ELISA Kits (CellTrend) in EGPA which fulfilled the 2022 ACR/EULAR classification criteria ( $n=10$ , table 1), systemic lupus erythematosus as disease control (SLE,  $n=47$ ) and healthy donors (HDs,  $n=220$ , SLE and HD demographics as published previously<sup>5</sup>). Antibody concentrations were calculated as arbitrary units (AUs) by extrapolation from a standard curve of 5 standards ranging from 2.5 to 40 AU/mL. Following informed consent, clinical data including vasculitis activity (Birmingham Vasculitis Activity Score (BVAS V3.0)), inflammatory markers (high-sensitivity C-reactive protein), MPO-ANCA and treatment were assessed at the time of serum sampling and during follow-up for 60 months.

In EGPA, anti-C5aR antibodies, but not anti-C3aR antibodies, were decreased compared with HD (anti-C3aR: EGPA vs HD:  $5.21 \text{ U/mL} \pm 2.43$  vs  $5.90 \text{ U/mL} \pm 2.61$ ,  $p=0.5168$ ; anti-C5aR:  $0.47 \text{ U/mL} \pm 4.17$  vs  $5.90 \text{ U/mL} \pm 2.91$ ,  $p=0.0049$ , figure 1A) and SLE (anti-C3aR: EGPA vs SLE:  $5.21 \text{ U/mL} \pm 2.43$  vs  $9.59 \text{ U/mL} \pm 9.18$ ,  $p<0.0001$ ; anti-C5aR:  $0.47 \text{ U/mL} \pm 4.17$  vs  $1.19 \text{ U/mL} \pm 10.05$ ,  $p=0.7588$ , figure 1A). No correlations were observed between anti-C3aR or anti-C5aR antibodies and concentrations of hsCRP, creatinine, BVAS and eosinophil count. Similar to GPA and MPA,<sup>5</sup> decreased anti-C5aR antibody concentrations below 0.45 U/mL were associated with major

relapse in EGPA at 12 months after baseline (HR: 11.29, 95% CI: 1.12 to 114.2,  $p=0.0401$ , figure 1B).

Here, we show that serum anti-C5aR antibody concentrations are associated with major relapse at 12 months in new-onset and relapsing EGPA. Possibly due to the smaller number of EGPA patients recruited in the present study and thus, contrasting with our study in GPA and MPA,<sup>5</sup> we found no association between a decrease in anti-C5aR antibodies and vasculitis activity in this study. Intriguingly, anti-C5aR antibody concentrations in EGPA were comparable to those previously found in GPA and MPA.<sup>4</sup> We hypothesise that similar to the findings in GPA and MPA,<sup>4</sup> decreased endogenous anti-C5aR antibody concentrations might reflect exhaustion through exaggerated complement activation. Experimental studies must further elucidate this aspect. Limitations of our study are the small number of patients included, contributing to large CIs and its cross-sectional design precluding definite conclusions other than that of decreased anti-C5aR antibody concentrations and association with major relapse found in the EGPA cohort presented herein. Further studies are needed to determine the role of endogenous antibodies on the C5a/C5aR-axis and complement activation in EGPA.

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**Patient consent for publication** Not applicable.

**Ethics approval** This study involves human participants and was approved by ethics committee of the University of Lübeck (Az 2023-113). Participants gave informed consent to participate in the study before taking part.

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