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# Cyclophosphamide induction dose and outcomes in ANCA-associated vasculitis with renal involvement
## A comparative cohort study

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**Abstract**

Treatment of ANCA-associated vasculitis (AAV) improved over the last decades but disease-unspecific agents such as cyclophosphamide are still associated with serious adverse events, including high rates of infectious complications and malignancy with increased mortality.

In this comparative cohort study, we included 121 AAV patients with renal involvement from 2 German vasculitis centers. Patients were separated into subsequent groups: 2.5 to 3 g vs >3 g cumulative cyclophosphamide induction dose. We investigated if a cyclophosphamide induction dose of 2.5 to 3 g could maintain efficacy while minimizing adverse events in AAV patients with renal involvement.

Patients with 2.5 to 3 g vs >3 g cumulative cyclophosphamide (median 3.0 g vs 5.5 g, $P < .001$) had a comparable time to remission (median 4.0 vs 3.8 months, log-rank $P = .87$) with 90.6% and 91.5% achieving remission after 12 months. Refractory disease was low in both groups (median 3.6% vs 6.2%, $P = .68$) and relapse rate did not differ (median 36% vs 42%, log-rank $P = .51$). Kidney function was comparable at disease onset in both groups (eGFR, mean $\pm$ SD 29 $\pm$ 20 mL/min/1.73 m$^2$ vs 35 $\pm$ 26 mL/min/1.73 m$^2$, $P = .34$) and improved after 2 years irrespective of the cyclophosphamide dose ($\Delta$eGFR, mean $\pm$ SD +8.9 $\pm$ 1.4 mL/min/1.73 m$^2$ vs +6.0 $\pm$ 1.1 mL/min/1.73 m$^2$, $P = .33$). The 2.5–3 g group had a lower rate of leukopenia (HR = 2.73 [95% CI, 1.2–6.3], $P = .014$) and less infectious episodes per patient (median 1.2 vs 0.7, $P = .012$), especially urinary tract infections (HR = 2.15 [95% CI, 1.1–4.5], $P = .032$).

A cyclophosphamide induction dose of 2.5 to 3 g was able to induce remission and prevent from relapses with fewer cases of leukopenia and less infectious episodes during follow-up. Especially elderly AAV patients who are particularly susceptible to infectious complications could benefit from minimizing dosing regimens with maintained efficacy to control disease activity.

**Abbreviations:** AAV = ANCA-associated vasculitis, CYC = cyclophosphamide, ESKD = end-stage kidney disease, GPA = granulomatosis with polyangiitis, HR = hazard ratio, IV = intravenous, MPO = myeloperoxidase, PR3 = proteinase 3, RTX = rituximab.

**Keywords:** ANCA-associated vasculitis, cyclophosphamide, infectious complications, leukopenia, renal involvement

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**Key Points**

- A cyclophosphamide induction dose of 2.5–3 g is sufficient to induce sustained remission with long-term preserved renal function compared with higher induction doses in AAV patients.
- The total number of infectious episodes and the incidence of leukopenia during follow-up are associated with increased cumulative cyclophosphamide induction dose.
- AAV patients who are particularly susceptible to infectious complications, such as AAV in the elderly, may benefit from further minimizing cyclophosphamide dosing while maintaining efficacy to control disease activity.

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# 1. Introduction

Survival of anti-neutrophil cytoplasmic autoantibody associated vasculitis (AAV) improved with the implementation of cyclophosphamide (CYC) and later rituximab (RTX) into induction therapy.[1,2] Current induction regimes are still limited by toxicity, causing adverse events with high long-term morbidity and mortality. Although the greatest threat after disease onset to patients with AAV is from treatment-related adverse events, active vasculitis especially in those patients with renal disease frequently hampers successful dose reduction.[3,4] The ultimate goal is safely minimizing dosing regimens with maintained efficacy to induce remission and prevent further relapses while reducing adverse events and associated morbidity.

The cumulative CYC induction dose of AAV patients was reduced during the last decade with the implementation of a pulsed intravenous (IV) application.[5] A reduced CYC induction dose seems to have fewer side effects but a higher relapse rate, whereas long-term follow-up revealed no differences neither in mortality nor in renal function.[5,6] Induction therapy with RTX has been proven equally effective to induce remission and control disease activity with comparable adverse events as a CYC-based regime even in AAV patients with renal involvement.[7,8]

Despite these improvements in tailoring AAV induction therapy, the cumulative CYC dosing investigated in clinical trials and administered in the daily clinical routine is still markedly higher than in other autoimmune disease with renal involvement as the proliferative lupus nephritis.[3,9] In the Euro-Lupus Nephritis Trial, low-dose IV CYC therapy with a cumulative dose of only 3 g safely induced remission with low numbers of adverse events.[9] Data of comparable CYC doses for induction therapy are lacking in AAV and require further assessment.

This study evaluated the efficacy of a cumulative CYC induction dose of 2.5 to 3 g on controlling AAV disease activity and preventing end-stage kidney disease (ESKD) during long-term follow-up. We also investigated the incidence of treatment-associated adverse events focusing on infectious complications.

# 2. Materials and methods

## 2.1. Patient groups and study design

We retrospectively included 121 patients with new-onset of granulomatosis with polyangiitis (GPA) or microscopic poly-angiitis from 2 German vasculitis centers between 2004 and 2019. One hundred and 3 patients were included at the University of Heidelberg, Department of Nephrology and 18 patients at the Clinical Center Ludwigshafen, Department of Internal Medicine A.

To investigate the impact of a reduced CYC dose for induction therapy on disease activity and adverse events, we compared patients with a cumulative CYC induction dose of 2.5 to 3 g (n = 56) to patients with >3 g (n = 65). Patients received CYC for induction therapy followed by maintenance therapy with azathioprine (AZA; 2 mg/kg body weight, orally) or mycophenolic acid (MMF; 2 g, orally) together with GC. In the 2.5 to 3 g group 23 patients received 2.5 g and 33 patients received 3 g cumulative CYC for induction therapy, respectively. The chosen CYC dose was clinically dependent on the practitioner who administered lower doses individually in both vasculitis centers. Due to the real-life clinical setting, low doses of 2.5 to 3 g could be investigated in this retrospective comparative cohort study. Patients with a cumulative CYC induction dose of <2.5 g were excluded. Further exclusion criteria were divergent induction or maintenance therapy, eosinophilic GPA, co-existent multisystem autoimmune disease and concurrent malignancy. Patients with less than 12 months observation time were excluded from the study except for patients who died within this time period.

The local ethics committee of the University of Heidelberg approved the trial (ref: S-624/2014). For the Clinical Center Ludwigshafen, no further approval was required according to the Landeskrankenhausgesetz (§36 and §37) of Rheinland-Pfalz, Germany. Both centers complied with the 1964 Declaration of Helsinki and subsequent amendments.

## 2.2. Definition of disease activity

The disease activity was assessed via the BVAS score (BVAS version 3) at initial diagnosis, after 3, 6, and 12 months and during relapse. Remission was defined as the absence of disease activity with a BVAS score of 0 under stable maintenance immunosuppressive therapy for at least 1 month with a prednisolone dose of ≤10 mg. A new or worsened manifestation of systemic vasculitis accompanied with a BVAS score of ≥1 was defined as a relapse. Refractory disease was defined as an unchanged or increased disease activity after 3 months of therapy or a chronic disease with presence of at least 1 major or 3 minor items of the BVAS score despite optimized immunosuppressive treatment and dosing.[10,11]

## 2.3. Baseline data and long-term follow-up

As baseline data we determined age, gender, observation time, affected organ systems and disease activity (Table 1). Kidney function was quantified at initial diagnosis, after 3, 6, and 12 months and after 2, 3, and 4 years by measurement of serum creatinine and glomerular filtration rate (estimated GFR, eGFR) estimated by the Modification of Diet in Renal Disease formula. The eGFR was defined as changes during the first 4 years compared to baseline values after obtaining stable remission.

Main outcomes were time to remission, relapse rate, refractory disease, incidence of ESKD, leukopenia and infectious complications, irreversible physical damage estimated by the vasculitis damage index,[12] death and death by infection.

**Table 1**

**Baseline demographics and clinical characteristics.**

|  | CYC >3g (N=65) | CYC 2.5–3g (N=56) | P |
|---|---|---|---|
| Diagnosis, N (%) |  |  |  |
| Granulomatosis with polyangiitis | 40 (62) | 31 (55) | .491 |
| Microscopic polyangiitis | 25 (38) | 25 (45) | .491 |
| Female sex, N (%) | 32 (49) | 28 (50) | .369 |
| BMI, median (IQR) | 25.7 (18.3–37.1) | 26.4 (19.1–43.2) | .553 |
| Age at diagnosis, mean±SD, y | 62±12 | 62±11 | .873 |
| ANCA ELISA or IIF, N (%) |  |  |  |
| PR3 | 39 (60) | 33 (59) | .364 |
| MPO | 23 (35) | 24 (43) | .400 |
| Double positive | 3 (5) | 3 (5) | .882 |
| Organ involvement, N (%) |  |  |  |
| General symptoms | 49 (75) | 45 (80) | .512 |
| Ears, nose, throat | 19 (29) | 10 (18) | .144 |
| Kidney | 65 (100) | 56 (100) | .999 |
| Lung | 38 (58) | 25 (45) | .129 |
| Nerve system | 9 (14) | 5 (9) | .399 |
| Organ systems involved, median (IQR) | 3 (2–4) | 2 (2–3) | .404 |
| Follow-up time, median (IQR), mo | 60 (20–96) | 55 (24–100) | .849 |
| BVAS at disease onset, median (IQR) | 18 (14–32) | 18 (14–21) | .669 |
| Kidney function at disease onset |  |  |  |
| Serum creatinine, mean±SD, mg/dl | 2.7±1.7 | 3.2±2.0 | .227 |
| eGFR, mean±SD, ml/min/1.73m$^2$ | 35±26 | 29±20 | .341 |
| Proteinuria, N (%) | 59 (91) | 54 (96) | .211 |
| Hematuria, N (%) | 60 (92) | 51 (91) | .806 |
| Dialysis at disease onset, N (%) | 7 (11) | 7 (13) | .767 |
| Induction therapy |  |  |  |
| **Cumulative CYC dose, median (IQR), g** | **5.5 (3.5–6.0)** | **3.0 (2.5–3.0)** | **<.001** |
| **Cumulative CYC dose per KG BW, median (IQR), mg** | **53.8 (40.2–73.0)** | **24.7 (18.4–31.2)** | **<.001** |
| **Duration of CYC induction, median (IQR), we** | **14 (12–18)** | **8 (6–15)** | **<.001** |
| Dosing interval, median (IQR), we | 2.3 (2.0–2.9) | 2.1 (1.8–2.6) | .682 |
| Steroid pulse therapy, N (%) | 50 (77) | 46 (82) | .480 |
| Plasma exchange, N (%) | 10 (15) | 9 (16) | .918 |
| Maintenance therapy |  |  |  |
| Azathioprine, N (%) | 44 (68) | 39 (70) | .818 |
| Mycophenolic acid, N (%) | 11 (17) | 8 (14) | .495 |
| Exclusively steroids, N (%) | 10 (15) | 10 (16) | .918 |
| Steroid dose at disease onset, median (IQR), mg | 60 (40–60) | 60 (40–60) | .854 |
| Steroid dose after 3 mo, median (IQR), mg | 16 (10–20) | 16 (8–20) | .808 |
| Steroid dose after 6 mo, median (IQR), mg | 6 (4–8) | 4 (4–10) | .462 |
| Duration of maintenance therapy, median (IQR), mo | 35 (22–48) | 27 (16–65) | .802 |

BVAS = Birmingham vasculitis activity score, BW = body weight, CYC = cyclophosphamide, eGFR = estimated glomerular filtration rate, IIF = indirect immunofluorescence, IQR = interquartile range, KG = kilogram, mo = months, SD = standard deviation, we = weeks.

### 2.4. Statistical methods

Data are expressed as median and interquartile range, mean± standard deviation (SD), or number (N) and percent (%). Continuous and categorial variables were performed using the nonparametric $t$ test with Well's correction or the Mann–Whitney $U$ test and the Chi-Squared test, respectively. Kaplan–Meier estimators and the log-rank test were used to determine the univariate probability of relapse-free survival and time to remission. Proportional hazards models were used for the incidence of adverse events with hazards ratios (HRs) and 95% CIs presented. Correlation of CYC doses with leukopenia was assessed by using Spearman's correlation analysis. Multiple logistic regression was used to detect independent associations between the CYC dosage and total infectious adverse events by controlling for confounders via multivariate modeling. Statistical significance was assumed at a $P$ value <.05. The statistical analyzes were performed using GraphPad Prism version 9.0.0 (GraphPad Software, San Diego CA, USA) and SPSS version 25 (IBM, Armonk NY, USA).

### 3. Results

#### 3.1. Study population and disease characteristics

Fifty six patients were in the 2.5 to 3 g CYC group with a median cumulative CYC dose of 3.0 g and a median duration of 8 weeks and 65 patients were in the >3 g group with a median cumulative CYC dose of 5.5 g ($P$ < .001) and a median duration of 14 weeks ($P$ < .001; Table 1). The CYC dose per kilogram body weight was also significantly higher in the >3 g group with a median of 53.8 mg compared to 24.7 mg in the 2.5 to 3 g CYC group ($P$ < .001). Baseline demographics, disease characteristics and maintenance therapy were comparable between both groups (Table 1). There

were no differences regarding disease categories of GPA and microscopic polyangiitis, organ involvement or disease activity (Table 1). The follow-up period was comparable between cohorts with a median of 55 months in patients with 2.5 to 3 g CYC and 60 months in patients with >3 g CYC (P=.85), respectively (Table 1).

### 3.2. Impact of cyclophosphamide induction dose on disease activity and long-term kidney function

We detected no differences in time to remission (4.0 vs 3.8 months, P=.87) with 90.6% and 91.5% achieving remission after 12 months in patients with 2.5 to 3 g compared to >3 g cumulative CYC dose (Fig. 1A). The disease activity was low after 3, 6, and 12 months in both groups (Fig. 1B, Table 2). Relapse rate (36% vs 42%, P=.51), time to relapse (28 vs 30 months, P=.98) and refractory disease (4% vs 6%, P=.68) were not significantly different (Fig. 1C, Table 2). The relapse-free survival was determined for PR3-AAV and MPO-AAV, separately. CYC dose had no impact on relapse-free survival neither in PR3- nor in



**Figure 1.** (A) Time to remission (%), (B) disease-activity as measured by BVAS score and (C) relapse-free survival (%) in PR3-positive and MPO-positive AAV patients with a cumulative CYC dose of 2.5 to 3 g compared to >3 g for induction therapy. PR3 and MPO double positive patients were excluded from relapse-free survival analysis.

MPO-positive patients (Fig. 1A). PR3-positivity was associated with a higher incidence of relapses compared to MPO-positivity (Fig. 1A).

After 4-year follow-up, kidney function as measured by eGFR (P=.57; Fig. 2A) was comparable between groups. In the 2.5 to 3 g group, 3 (5%) patients developed ESKD compared to 5 (8%) patients in the >3 g group (P=.61; Fig. 2B).

### 3.3. Impact of cyclophosphamide induction dose on leukopenia, infectious complications, irreversible physical damage and mortality

Patients treated with >3 g CYC had a higher incidence of leukopenia (Fig. 3A). During follow-up, 19 (29%) vs 6 (11%) patients developed leukopenia with a HR of 2.73 [95% CI, 1.2–6.3] (P=.014). In both groups, leukopenia mainly occurred during the first 12 months after initiation of induction therapy. The cumulative CYC dose for induction therapy correlated with the incidence of leukopenia ($r_s$=0.28, P=.002). Total infectious episodes per patient during follow-up were higher in the >3 g group with a median of 1.2 vs 0.7 (P=.012; Table 2; Fig. 3B). At least one infectious complication occurred in 57% of patients with >3 g and in 36% of patients with 2.5 to 3 g CYC (P=.020). This was mainly caused by more urinary tract infections especially during the first 12 months after initiation of induction therapy with a HR of 2.2 [95% CI, 1.1–6.2] (P=.034; Fig. 3C). We evaluated the impact of different CYC doses on total infectious adverse events by controlling for confounders as age, disease activity and kidney function by multivariate modeling (see, Supplemental Digital Content Table S1, which demonstrates the multivariate modeling, http://links.lww.com/MD/G300). The CYC induction dosage and age independently correlated with more infectious complications during follow-up (OR of 4.4 [95% CI, 1.3–20.3] and OR of 0.19 [95% CI, 0.1–0.6]). The incidence of pneumonia (P=.07), herpes virus infection (P=.56) and sepsis (P=.28) were not significantly different between groups.

The median vasculitis damage index was 1.0 in the >3 g CYC group compared to 1.0 in the 2.5 to 3 g CYC group (P=.86). Death during follow-up (P=.49) or death by infection (P=.25) were not significantly different between CYC groups. Seven patients of the >3 g CYC group died during follow-up including 3 patients with death by infection compared to 4 deaths during follow-up with no deaths by infection in the 2.5 to 3 g CYC group.

## 4. Discussion

Treatment-related toxicity with high long-term morbidity and mortality still counteracts advances of CYC induction regimes in AAV which improved patient and renal survival significantly. Strategies to reduce CYC-related adverse events included the reduction of duration and dose, changes to alternative application forms or switching to alternative immunosuppressive regimes.[5,6,8] However, for many patients with AAV, CYC remains the mainstay of induction therapy. Despite improvements in tailoring CYC induction therapy, commonly administered CYC doses in the daily clinical routine are still notably higher than in other autoimmune disease with renal involvement as the proliferative lupus nephritis.[3,9] In our study we investigated, if a cumulative CYC dose of only 3 g could maintain disease control while minimizing adverse events in AAV patients with renal involvement.
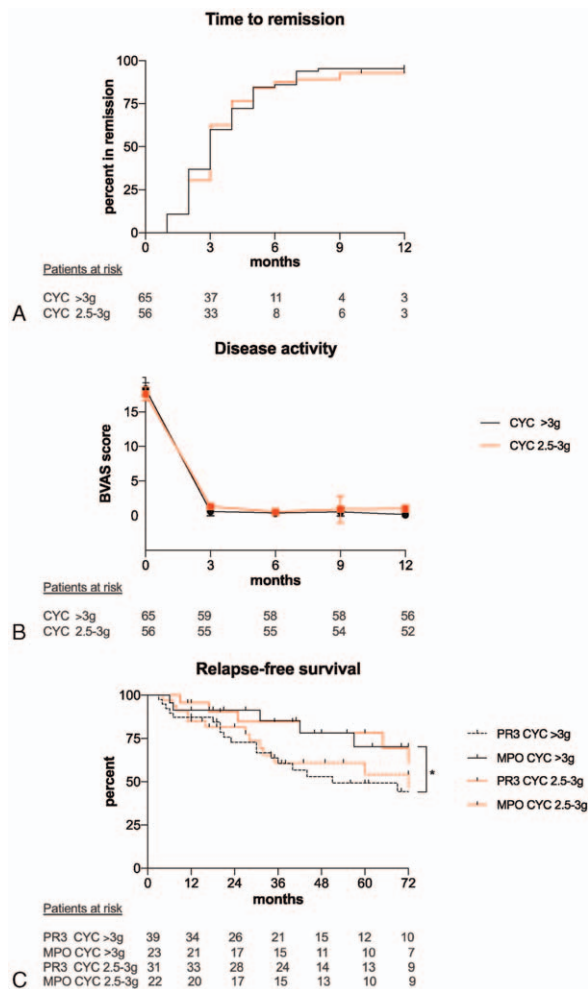
**Table 2**

**Outcomes and complications.**

| | CYC >3 g (N=65) | CYC 2.5–3 g (N=56) | P |
|---|---|---|---|
| Relapse rate, N (%) | 27 (42) | 20 (36) | .512 |
| Time to relapse, median (IQR) | 30 (7–51) | 28 (11–56) | .978 |
| Refractory disease, N (%) | 4 (6) | 2 (4) | .679 |
| Disease activity | | | |
| BVAS after 3 mo, median (IQR) | 0 (0–0) | 0 (0–0) | .918 |
| BVAS after 6 mo, median (IQR) | 0 (0–0) | 0 (0–0) | .967 |
| BVAS after 12 mo, median (IQR) | 0 (0–0) | 0 (0–0) | .396 |
| Kidney function | | | |
| Serum creatinine after 3 mo, mean±SD, mg/dL | 1.6±1.0 | 1.5±0.5 | .411 |
| eGFR after 3 mo, mean±SD, ml/min/1.73 m$^2$ | 50±19 | 51±22 | .633 |
| Serum creatinine after 6 mo, mean±SD, mg/dL | 1.6±0.8 | 1.5±0.7 | .908 |
| eGFR after 6 mo, mean±SD, ml/min/1.73 m$^2$ | 52±22 | 53±20 | .941 |
| Serum creatinine after 1 a, mean±SD, mg/dL | 1.5±0.8 | 1.4±0.4 | .729 |
| eGFR after 1 a, mean±SD, ml/min/1.73 m$^2$ | 56±24 | 56±18 | .897 |
| Serum creatinine after 2 a, mean±SD, mg/dL | 1.6±1.2 | 1.3±0.4 | .474 |
| eGFR after 2 a, mean±SD, ml/min/1.73 m$^2$ | 58±27 | 59±18 | .807 |
| Serum creatinine after 3 a, mean±SD, mg/dL | 1.7±1.1 | 1.3±0.4 | .726 |
| eGFR after 3 a, mean±SD, ml/min/1.73 m$^2$ | 53±23 | 59±19 | .505 |
| Serum creatinine after 4 a, mean±SD, mg/dL | 1.3±0.8 | 1.2±0.3 | .175 |
| eGFR after 4 a, mean±SD, ml/min/1.73 m$^2$ | 64±22 | 64±16 | .573 |
| ESKD, N (%) | 5 (8) | 3 (5) | .606 |
| Infectious complications during the first 24 mo | | | |
| **At least 1 infectious complication, N (%)** | **37 (57)** | **20 (36)** | **.020** |
| **Infectious episodes per patient, median (IQR)** | **1.2 (0–2)** | **0.7 (0–1)** | **.012** |
| **Urinary tract infection, N (%)** | **20 (31)** | **8 (14)** | **.032** |
| Pneumonia, N (%) | 12 (18) | 4 (7) | .067 |
| Opportunistic pneumonia, N (%) | 4 (6) | 2 (4) | .514 |
| Herpes virus infections, N (%) | 6 (9) | 8 (14) | .563 |
| Sepsis, N (%) | 6 (9) | 2 (4) | .284 |
| **Leukopenia, N (%)** | **19 (29)** | **6 (11)** | **.014** |
| VDI after 1 year, median (IQR) | 1.0 (0–1) | 1.0 (0–1) | .863 |
| Death during follow-up, N (%) | 7 (11) | 4 (7) | .489 |
| Death by infection, N (%) | 3 (5) | 0 (0) | .248 |

a, years; BVAS = Birmingham vasculitis activity score, CYC = cyclophosphamide, ESKD = end-stage kidney disease, eGFR = estimated glomerular filtration rate, IQR = interquartile range, mo = months, SD = standard deviation, VDI = vasculitis damage index.

Both groups with a median cumulative CYC dose of 3.0 g vs 5.5 g controlled disease activity to a comparable content with 93.8% and 92.9% achieving remission after 12 months and a relapse rate of 36% and 42%, respectively. PR3-positivity was associated with a significantly higher incidence of relapses compared to MPO-positivity, which has already been described by us and others.[4,13] A long-term follow-up of the CYCLOPS trial revealed a lower risk to relapse in a daily oral group with a cumulative CYC dose of 15.9 g vs an IV group with only 8.2 g. At least 1 relapse occurred in 20.8% (daily oral group) vs 39.5% (IV group) of AAV patients, respectively. A meta-analysis and review by de Groot et al additionally indicated a high remission induction rate but slightly more relapses in patients with lower cumulative CYC doses administered IV compared to a daily oral regime.[1] Our 2.5 to 3 g CYC group showed comparable relapse rates to IV CYC regimens in previous studies, but with a markedly lower CYC dose.[6,14–16] With a median of 5.5 g, even the patients in our >3 g group received a significantly lower cumulative CYC dose than applied in previous studies.[5–7,15–16] Although higher cumulative doses administered in the daily oral era were associated with a lower risk of relapse, this did not result in differences in kidney or patient survival during long-term observation.[5,6] This is consistent with our observations, in which renal function improved during 4-year follow-up regardless of the cumulative CYC dose and mortality was not different between groups.

Leukopenia constitutes an important issue in CYC induction therapy and an association with increased mortality and more infectious complications has been demonstrated.[17,18] The risk of severe leukopenia was significantly increased in patients with high CYC doses, especially in the daily oral era.[5,6] The cumulative CYC dose in our study directly correlated with leukopenia and AAV patients in the 2.5 to 3 g group had a significantly lower incidence during follow-up. Only 11% developed leukopenia, significantly less patients compared to the >3 g group or previous trials.[6] The total number of infectious episodes was also higher in AAV patients with >3 g CYC, mainly due to more urinary tract infections. This is in line with recent literature, where higher CYC induction doses were associated with an earlier occurrence and increased total burden of infections.[19] Since age was related to more infectious complications as shown in our and recent studies, especially older AAV patients may benefit from a further reduced CYC dose.[20] Safely controlling disease activity with less leukopenia and infectious complications could lower mortality in such risk cohorts.
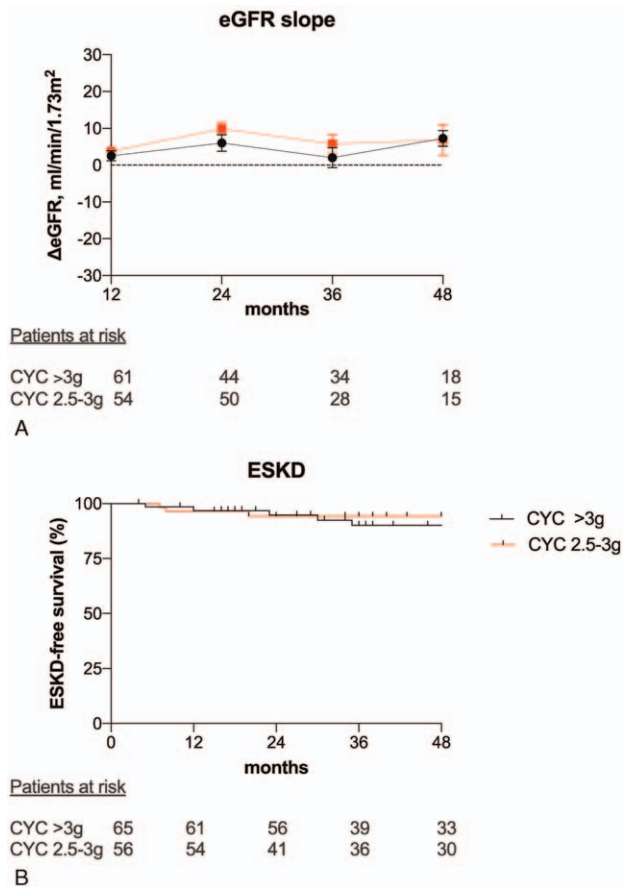
**Figure 2.** (A) eGFR slope and (B) ESKD-free survival in AAV patients with a cumulative CYC dose of 2.5 to 3 g compared to >3 g for induction therapy.

RTX is another agent that has been proven effective in inducing remission in AAV. Two subsequent trials demonstrated non-inferiority of RTX to CYC for remission induction.[21,22] The sustained remission rates were high with both RTX and CYC but the RTX based regime was not associated with reduction in severe adverse events.[2,22,23] Even among patients with severe renal disease or alveolar hemorrhage the outcomes were comparable.[8] However, CYC doses administered in comparative studies were significantly higher than in our study and leukopenia was increased within the CYC groups, which could be a risk factor especially for vulnerable patient populations.

Our study has few limitations. The study is designed retrospectively and less common adverse events such as cardiovascular disease, cancer or hemorrhagic cystitis could not be assessed properly. In addition, the examined subgroups had different patient numbers with fewer patients in the 2.5 to 3 g group. There was no standardized therapeutic protocol for both GC and CYC tapering, and the CYC and GC doses chosen were clinically dependent on the practitioner at both vasculitis centers. Another limitation is a possible underestimation of infectious complications due to underreporting of other physicians outside the center setting.

This study suggests that a CYC induction dose of 2.5 to 3 g could be able to induce remission and prevent from relapses with fewer cases of leukopenia and less infectious episodes during follow-up. Especially high-risk patients, such as AAV in elderly patients, could benefit from even lower cumulative CYC doses with maintained efficacy to control disease activity and preserved kidney function while reducing adverse events and associated morbidity.
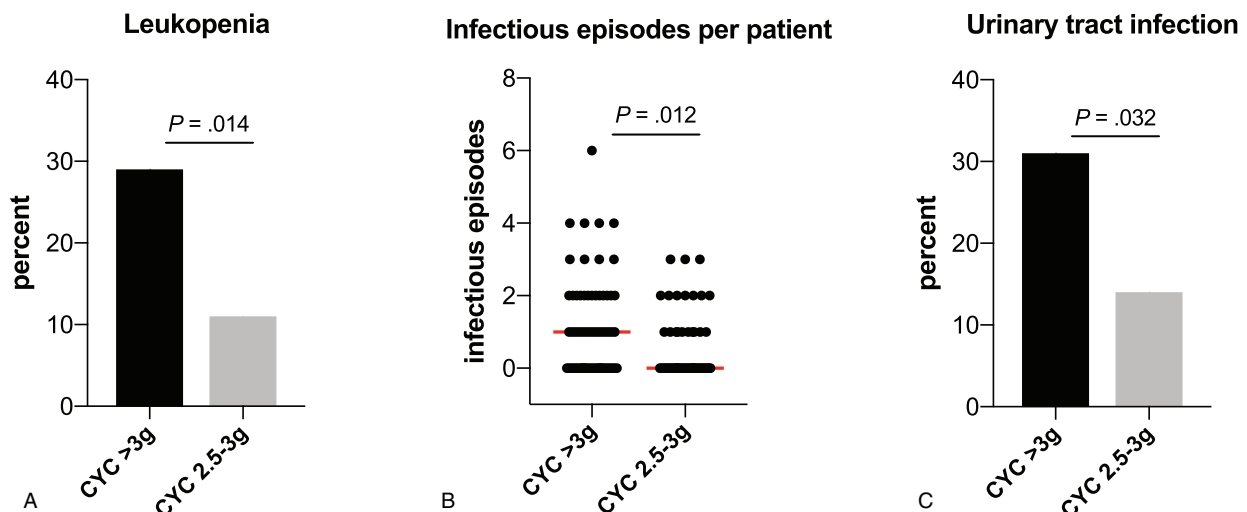
## Author contributions

**Figure 3.** (A) Leukopenia, (B) infectious episodes per patient and (C) incidence of urinary tract infection in AAV patients with a cumulative CYC dose of 2.5 to 3 g compared to >3 g for induction therapy.

**Investigation:** Claudius Speer, Matthias Schaier.

**Methodology:** Claudius Speer.

**Project administration:** Claudius Speer.

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**Supervision:** Christian Morath, Martin Zeier, Raoul Bergner, Matthias Schaier.

**Validation:** Martin Zeier.

**Writing – original draft:** Claudius Speer, Paula Reichel, Matthias Schaier.

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