RANDOMIZED CONTROLLED TRIAL OF PROLONGED TREATMENT IN THE REMISSION PHASE OF ANCA-ASSOCIATED VASCULITIS

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ABSTRACT

Objectives:

A prospective randomized trial to compare two different durations of maintenance immunosuppressive therapy for the prevention of relapse in ANCA-associated vasculitis (AAV).

Methods:

AAV patients were recruited 18-24 months after diagnosis if they were in stable remission after cyclophosphamide/prednisolone-based induction followed by azathioprine/prednisolone maintenance therapy. They were randomized (1:1) to receive continued azathioprine/prednisolone to 48 months from diagnosis (continuation group) or to withdraw azathioprine/prednisolone by 24 months (withdrawal group). The primary endpoint was the relapse risk, from randomization to 48 months from diagnosis.

Results:

One hundred and seventeen patients were randomized and 110 remained to the trial end. At entry, median serum creatinine was 116 μmol/l (range 58-372), 53% were ANCA positive. The percentage of patients presenting with relapse was higher in the withdrawal than in the continuation treatment group (63% vs 22%, $p<0.0001$, OR 5.96, 95%CI 2.58-13.77). ANCA positivity at randomization was associated with relapse risk (51% vs 29%, $p=0.017$, OR 2.57, 95%CI 1.16-5.68). Renal function, ANCA specificity, vasculitis type and age were not predictive of relapse. Severe adverse events were more frequent in the continuation than withdrawal groups (9 vs 3 events) but the continuation group had better renal outcome (0 vs 4 cases of end stage renal disease), with no difference in patient survival.

Conclusions:

Prolonged remission maintenance therapy with azathioprine/prednisolone, beyond 24 months after diagnosis, reduces relapse risk out to 48 months and improves renal survival in AAV.

INTRODUCTION

ANCA-Associated Vasculitides (AAV) are a group of autoimmune systemic diseases that are associated with a necrotizing, pauci-immune, vasculitis of small blood vessels and the presence of circulating autoantibodies to myeloperoxidase (MPO-ANCA) or proteinase 3 (PR3-ANCA). The major subgroups of AAV are microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA, Wegener's) and eosinophilic granulomatosis with polyangiitis (EGPA)[1]. Renal involvement is manifested by a necrotizing, crescentic glomerulonephritis and results in end stage renal disease (ESRD) in up to 20% of patients[2].

Therapeutic management of MPA and GPA is divided into induction and maintenance phases. Remission induction is achieved in most cases with cyclophosphamide or rituximab in combination with high dose glucocorticoids and sometimes plasma exchanges, while remission maintenance regimens have employed an oral immunosuppressive, such as azathioprine or methotrexate, or repeat dose rituximab, with or without low dose glucocorticoids[3,4]. The optimal duration of remission maintenance therapy remains unknown, with current consensus recommendations suggesting at least 24 months, once remission has been obtained[5].

Relapse occurs in 30-50% of patients by five years and has been associated with a diagnosis of GPA, PR3-ANCA specificity, the presence of ear nose and throat involvement, persisting ANCA positivity after induction therapy, a lower serum creatinine at diagnosis, and withdrawal of glucocorticoids or immunosuppressives[6]. The consequences of relapse are additional accrual of disease and treatment related damage and morbidity, and renal relapse is associated with an increased risk of ESRD[7]. Continuing remission therapy increases exposure to the toxicities of immunosuppressives and glucocorticoids.

This study tested whether continued azathioprine/prednisolone was more effective in preventing relapse than their withdrawal at 24 months from diagnosis in AAV patients.

METHODS

Study Design and Patients

We hypothesized that prolonged maintenance therapy with low-dose prednisolone and azathioprine reduces the frequency of relapse, when compared with withdrawal of immunosuppression two years after diagnosis. This trial (REMAIN) was conducted

by the European Vasculitis Society (EUVAS) and recruited patients from 33 centers, in 11 European countries. The study was approved by the local ethics committee in each participating center and all patients provided written informed consent, according to the Declaration of Helsinki.

Criteria for inclusion were (1) a diagnosis of MPA, GPA or renal-limited vasculitis. (2) Renal involvement and/or other threatened loss of function of a vital organ (lung, brain, eye, motor nerve, or gut); and ANCA positivity; ANCA-negative patients were eligible for enrollment in the study only when there was histologic confirmation of pauci-immune vasculitis. (3) Remission-induction therapy with cyclophosphamide and prednisolone for at least 3 months, with or without plasma exchanges. (4) Stable remission on azathioprine/prednisolone. They were recruited and randomized 18 to 24 months from commencement of therapy.

Exclusion criteria were age under 18, pregnancy, previous malignancy, known HIV infection, previous life-threatening relapse, end-stage renal disease (ESRD) at inclusion and allergy to study medications. Patients not in stable remission for at least six months at 18 months after commencement of therapy and patients who had discontinued azathioprine and/or prednisolone were excluded from the study.

Disease definitions

Diagnostic definitions were initially based on the 1994 Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitides[8] and re-evaluated after completion of the study, according to the recently revised criteria[1]. Remission was defined as a 1994 Birmingham Vasculitis Activity Score (BVAS) of 0, indicating the absence of new or worse disease activity, with persistent disease activity for no more than one item [9]. Major relapse was defined by the recurrence or first appearance of at least 1 of the 24 items of the Birmingham Vasculitis Activity Score, that are indicative of threatened function of a vital organ (kidney, lung, brain, eye, motor nerve, or gut) attributable to active vasculitis. Minor relapse was defined by the recurrence or first appearance of at least three other BVAS items. Determinations of remission and relapse were made by the investigator and validated retrospectively by an independent observer.

Drug regimens

Patients were randomly assigned at entry, 18 to 24 months after initiation of immunosuppression, in a 1:1 ratio, to continuation or withdrawal treatment groups (Table 1).

Table 1: Drug doses according to treatment arm

Months from randomization	Continuation arm		Withdrawal arm	
	Prednisolone mg/day	Azathioprine mg/kg/day	Prednisolone mg/day	Azathioprine mg/kg/day
0	5-7.5	1	5	0.75
1	5-7.5	1	4	0.75
2	5-7.5	1	4	0.75
3	5	1	2	0
4	5	1	1	0
5	5	1	0	0
12	5	1	0	0
18	4	1	0	0
19	4	1	0	0
20	3	1	0	0
21	3	1	0	0
22	2	1	0	0
23	1	1	0	0
24	0	1	0	0
30	0	1	0	0

Evaluations

Study assessments were performed at entry, then every three months until 30 months from entry for non-relapsing patients and until the time of relapse for relapsing patients. The assessments included BVAS[9], serum creatinine, C-reactive protein, ANCA positivity (requiring both positivity by indirect immunofluorescence and by PR3-ANCA or MPO-ANCA assay, performed in local laboratories), drug doses and adverse events. Glomerular filtration rate (eGFR) was estimated using the MDRD formula[10]. All cause damage since the vasculitis diagnosis was assessed by the Vasculitis Damage Index (VDI)[11] at entry then every six months to the trial end.

End points

The primary end-point was the percentage of patients presenting a relapse of vasculitis, including major and minor relapses, during the study period. Secondary end-points were incidence of major and minor relapses, mortality, adverse events of therapy, rise in cumulative damage score (VDI), deterioration of eGFR, incidence of ESRD and ANCA status during follow-up.

Statistical analysis

Randomization was performed centrally. Treatment allocation was done by block

randomization (permuted blocks of four), per country. Primary data were collected locally in record books and subsequently submitted for centralized validation and analysis.

Based on a 1-tailed design, with a significance level of 5% and a power of 0.8, the inclusion of 116 patients was required to demonstrate a 20% lower relapse rate in the maintenance therapy group during the study period (assuming a 3-fold increase of relapse risk in the discontinuation arm).

The demographic characteristics of the two groups were compared with the use of Student's t-test or a Wilcoxon rank-sum test for continuous measures and a chi-square test or Fisher's exact test for categorical variables. The effect of treatment on time to relapse was examined by Kaplan–Meier analysis, with the use of the log-rank test. The two groups were compared in terms of the secondary end-points reached between the time of remission and the end of the study. The rates of adverse events were compared with the use of two-by-two tables and Fisher's exact test. The values of eGFR and VDI were compared with the use of the Wilcoxon rank-sum test.

RESULTS

Patients

Between September 1998 and March 2010, 121 patients were enrolled. Four were excluded due to ineligibility, because of early relapse (n=3) or malignancy (n=1). One hundred and seventeen were randomized with a mean period of 18.8±1.8 months after initiation of induction therapy: 61 to the continuation and 56 to the withdrawal groups. During the study, three patients withdrew (patient's choice (n=2) or physician's decision (n=1)) and 4 were lost to follow-up (Figure 1). Complete data for analysis were available for 110 patients.

Demographic characteristics of the study population are detailed in Table 2. Fifty-two patients (47%) had GPA and 58 (53%) had MPA. ANCA specificity was PR3 in 52% of cases, MPO in 44%, whereas ANCA were negative or without specificity in 4%. Almost all patients (96%) were enrolled in this study after the first remission of newly diagnosed AAV. The median follow-up was 925 days (IQR 878-970), after randomization.

Table 2: Demographics of randomized patients according to treatment arm, 18-24 months after diagnosis

Variable	Continuation group (n=59)	Withdrawal group (n=51)	p-Value
Age (years)	57.7±14.1	57.4±14.3	0.89
Sex (%)			0.69
Male	49	53	
Female	51	47	
AAV type (%)			0.96
GPA	47	47	
MPA	53	53	
ANCA at diagnosis (%)			0.11
PR3	46	59	
MPO	47	41	
Negative	7	0	
Delay from diagnosis (months)	18.6±0.2	19.0±0.2	0.28
Serum creatinine (μmol/l)	140±67	129±54	0.34
eGFR (ml/min/1.73m^2)	51.6±23.0	55.8±23.4	0.34
ANCA			0.59
positive	51%	56%	
negative	49%	44%	
Prednisolone dose (mg/day)	5.8±2.3	5.9±2.1	0.61
Azathioprine dose (mg/day)	102±35	95±39	0.27
VDI	1.8±0.2	1.8±0.2	0.98

AAV (ANCA-associated vasculitis), GPA (granulomatosis with polyangiitis), MPA (microscopic polyangiitis), PR3 (proteinase 3), MPO (myeloperoxidase), S Creat (serum creatinine), eGFR (estimated glomerular filtration rate), VDI (Vasculitis Damage Index). Values are given as means±standard deviations.

Protocol treatment

At randomization, the mean daily azathioprine dose was 99±37 mg and the mean daily prednisolone dose was 5.9±2.2 mg. Immunosuppression was rapidly tapered according to the study protocol in the withdrawal group, whereas it was continued until the end of study in the continuation group. Median and mean daily doses of azathioprine and prednisolone are detailed in Supplemental figures 1a and 1b.

Efficacy assessment

Primary end-point

Thirty-two patients (62.7%) in the withdrawal group experienced a relapse as

compared with 13 (22.0%) in the continuation group (log rank test p<0.0001) (Figure 2a). The patients in the withdrawal group had a 2.84-fold higher relative risk of relapse (95%CI 1.72-4.9), when compared to patients continuing immunosuppression. Interestingly, 78% of relapses in the withdrawal group occurred after removal of azathioprine vs 8% in the continuation group. The median daily azathioprine dose at relapse was 75 mg (IQR 50-100) mg in the continuation group vs 0 mg (IQR 0-0) in the withdrawal group.

Of note, primary endpoint difference between treatment groups remained highly significant (p<0.001) if we excluded patients of the withdrawal group that continued small doses of azathioprine beyond month 6 (n=5) or if we included patients that withdrew their consent or were lost to follow-up (n=7).

Secondary end-points

A major relapse occurred in 18 patients (35.3%) of the withdrawal and in eight (13.5%) of the continuation groups (p=0.007) (Figure 2b). The estimated GFR at last follow-up was 52.5±26.7 ml/min/1.73m^2 in the withdrawal and 54.1±24.7 ml/min/1.73m^2 in the continuation groups (p=0.78). Nevertheless, the ΔeGFR between randomization and end of study in the withdrawal group was -3.3±14.9 ml/min/1.73m^2 whereas it was +2.5±9.8 ml/min/1.73m^2 in the continuation group (p=0.01). This difference was not found when the analysis was restricted to patients that had completed follow-up without relapse (+0.8±15.4 vs +2.6±8.0 ml/min/1.73m^2, p=0.53). Four patients (7.8%) of the withdrawal group developed ESRD during follow-up as compared with none in the continuation group (p=0.012). Of note, median eGFR at randomization, for these 4 patients, was 29.5 ml/min/1.73m^2 (range 15-59). There were two deaths (3.9%) in the withdrawal and five (8.5%) in the continuation groups (p=0.32). Causes of death were cancer in 3 cases, cardiovascular disease in 2, undetermined for 2 patients.

Although there was no difference in the percentage of ANCA-positive patients at randomization (51% in the continuation versus 56% in the withdrawal groups), patients in the withdrawal group had more frequent reappearance of ANCA after randomization. By month 6, 72% of patients in the withdrawal group were ANCA positive compared with 52% in the continuation group (p=0.04) (Supplemental Figure 2a). There was no difference in the final VDI score between the two groups (Supplemental Figure 2b).

Predictors of relapse

Univariate analysis revealed that withdrawal of immunosuppression (p<0.0001) and ANCA positivity at randomization (p=0.017) were the only predictors of relapse during follow-up (Fig 2c, Table 3). Multivariate analysis confirmed these factors were independently associated with risk of relapse. ANCA specificity at diagnosis (PR3 vs MPO), disease phenotype (GPA vs MPA), age or renal function at randomization, were not predictive of relapse in this study. Similar results were obtained when studying the risk of major relapse during follow-up.

Table 3: Risk factors associated with AAV relapse

	Subgroup	Relapse Risk	p-value	Odds-ratio (95%CI)
Treatment arm	W	32/51 (63%)	<0.0001	5.96 (2.58-13.77)
	C	13/59 (22%)		
ANCA specificity at diagnosis	PR3	28/57 (49%)	0.13	1.82 (0.83-3.98)
	MPO	17/49 (35%)		
ANCA testing at randomization	Positive	30/58 (51%)	0.017	2.57 (1.16-5.68)
	Negative	15/51 (29%)		
Disease	MPA	22/58 (38%)	0.5	0.77 (0.36-1.65)
	GPA	23/52 (44%)		

AAV (ANCA-associated vasculitis), GPA (granulomatosis with polyangiitis), MPA (microscopic polyangiitis), PR3 (proteinase 3), MPO (myeloperoxidase), W (withdrawal subgroup), C (continuation subgroup)

Kaplan-Maier analysis shows that the difference between survival according to treatment arm persists across different subgroups of patients, such as patients with MPO or PR3 ANCA specificity (Supplemental Figure 3a), as well as in patients with or without ANCA positivity at randomization (Supplemental Figure 3b).

Severity of relapse

Characteristics of the relapses occurring during the study period are detailed in Suppl. table 1. Relapse severity was not different between treatment arms. Mean BVAS at relapse was 7.1±4.1 in the withdrawal group and 8.7±4.4 in the continuation group (p=0.29). Organ involvement at relapse was not different between the two groups, except ENT involvement, which was more frequent in the continuation group (69% vs 34%, p=0.048).

Adverse events

Seventy-one adverse events were reported in 46 patients (Table 4). Severe or life-threatening adverse events occurred in 13 (12%). There was no statistical difference between the two groups in the prevalence or severity of adverse events. The most frequent events were infections, occurring in 13 (22%) patients of the continuation and 10 (19%) of the withdrawal group. Hematological disorders and cardiovascular events were more frequent among patients of the continuation group.

Table 4: Adverse events (AE)

Variable	Continuation group (n=59)	Withdrawal group (n=51)	p-Value
Total number of AE	43	28	0.07
Number (%) of patients with at least one AE	26 (44%)	20 (39%)	0.69
Number (%) of patients with ≥ grade 3 AE	9 (15%)	3 (6%)	0.13
Type of AE			
Cancer	7	4	0.54
Non-melanoma skin cancer	2	2	0.99
Infection	17	13	0.83
Cytopenia	7	1	0.066
Hepatitis	2	2	0.99
Cardiovascular events	5	0	0.060

Adverse events were classified according to the v3.0 Common Terminology Criteria for Adverse Events (CTCAE)

DISCUSSION

ANCA-associated vasculitis carries a substantial and often unpredictable risk of relapse, and prolonged relapse prevention therapy is recommended that may itself contribute to organ damage, morbidity and patient mortality[7]. We have shown that continuation of treatment with azathioprine and prednisolone beyond 24 months from diagnosis was more effective at preventing relapse than withdrawal of these agents for AAV patients with GPA/MPA. These results confirm the ability of the azathioprine/prednisolone combination to influence relapse risk and suggest that treatment should be continued for at least 48 months from diagnosis, especially in those with persistent ANCA positivity after induction therapy.

Despite the use of azathioprine/prednisolone-based remission-maintenance therapy, the risk of relapse after induction of remission with cyclophosphamide, was 38% at 5 years in the recent meta-analysis of previous EUVAS trials[6]. This risk remains high

when rituximab is given for induction of remission instead of cyclophosphamide, with a 32% risk of relapse at month 18[12]. Previous relapse prevention studies in AAV have demonstrated an equivalence of methotrexate to azathioprine, a lower efficacy with mycophenolate mofetil, and no efficacy of etanercept[13-15]. In view of the high proportion of patients with renal disease in this study, azathioprine was selected over methotrexate. Repeat dose rituximab has recently been shown to be superior at preventing relapse than azathioprine[16], but this drug was not is use in AAV at the time this trial was designed.

The optimal duration of immunosuppressive therapy after induction of remission is unknown. Only one previous study has compared different regimens, in patients with persistent anti-PR3 ANCA positivity at remission. Sanders et al[17], randomized 45 patients to receive either standard (1 year after diagnosis and subsequent tapering) or extended (4 years after diagnosis and tapered thereafter) azathioprine maintenance therapy. Although 46% of patients relapsed in the standard therapy group vs 24% in the extended therapy group, the difference was not statistically different.

This study clearly demonstrates that continuation of glucocorticoids and azathioprine beyond two years is associated with a 3-fold reduction of relapse risk. Moreover, extension of immunosuppression is associated with a better renal survival, as illustrated by the fact that all patients that reached ESRD during follow-up, had discontinued azathioprine a few months before. Of note, previous studies have shown that every renal relapse is associated with an eGFR decrease of 8-12 ml/min[18,19] and that those patients are 4.7 times more likely to progress to ESRD[20].

The overall frequency of relapse seen in this study, 41% at 48 months, was similar to that reported in other AAV studies (46% in the IMPROVE trial[14], 35% in the WEGENT trial[13], 45% in the azathioprine arm of the MAINRITSAN trial)[16]. The relapse risk in the withdrawal group of the this study (62.7%) was much higher, but in those studies the follow-up period was less than 12 months, after cessation of immunosuppression. Interestingly, there was good compliance of clinicians to the study drug regimen in the withdrawal group and even a trend to under-dosing in the continuation group that may have reduced the magnitude of the treatment effect of azathioprine/prednisolone. The relative contributions of azathioprine or prednisolone

to the treatment effect are not known, although an earlier systematic review has highlighted the increase in relapse risk that follows glucocorticoid withdrawal[6].

In our study, continuation of immunosuppressive therapy was associated with more frequent adverse events such as malignancies or infections. The safety profile was not statistically different between the two groups, but our study was underpowered to detect significant differences in adverse events between groups. Importantly, patient survival as well as VDI score - which reflects the cumulative organ damage due to vasculitis and/or treatment - was similar. Of note, the final VDI score in the whole study population was 2.2, similar to that described (2.66) in the long-term follow-up of the EUVAS trials[7]. Despite small numbers, we found that cytopenias and cardiovascular complications were more common in the continuation group, possibly in relation with the known toxicity of azathioprine and the metabolic effects of glucocorticoids.

The main question raised by this study is whether we should recommend an extended duration of immunosuppression for all AAV patients after achievement of sustained remission. Numerous studies have demonstrated that the risk of relapse is more important among patients with GPA and/or anti-PR3[6,21], suggesting that this subgroup of patients should receive prolonged immunosuppressive therapy. Our study was underpowered to confirm this hypothesis (Supplemental Fig 3a). Nevertheless, our data show that persistent ANCA positivity, two years after initiation of immunosuppression predicts a higher risk of relapse, suggesting that this subgroup of patient may require a different immunosuppressive regimen. Other studies have observed a reduced risk of relapse was associated with negativity of ANCA at the time of switching to maintenance therapy[22,23]. On the other hand, in our study, relapse occurred in 29% of patients with negative ANCAs at randomization, when assigned to AZA discontinuation (fig 3b), revealing that even those patients have an important risk of relapse when stopping too early the immunosuppressive drugs. Of note, 83% of relapsing patients with ANCA negativity at inclusion had positive ANCA testing at relapse.

Our study has several limitations. First, this trial was open-label and the absence of placebo might have lead to overestimation of the relapse rate in patients having discontinued azathioprine and corticosteroids. BVAS is a semi-objective tool although many relapses were renal assessed by objective criteria. Nevertheless, prognosis was still different between the two groups, even when robust criteria were

used to define severe flare of disease or ESRD. Second, this study was designed and conducted before widespread use of rituximab and it is difficult to extrapolate these results to patients receiving B-cell depleting agents as induction and/or maintenance therapy. Further studies are determining if, similarly to what we have shown with azathioprine, an 18-months duration is less effective than a 48-months maintenance therapy with RTX, for prevention of AAV relapse (MAINRITSAN 3 trail, NCT02433522). Third, the study design may have induced some bias in the study population, excluding patients with intolerance to azathioprine but also patients with more severe disease, such as patients with life-threatening vasculitis or patients that experienced early relapse, during the initial 18-months azathioprine therapy preceding randomization. We did not have detailed information from diagnosis to precisely describe organ distribution such as ENT or cardiovascular involvement, baseline renal function, cyclophosphamide exposure (total dose, i.v./oral administration), factors known to influence relapse risk. Four, the 12-years duration of study enrollment could have influenced the results. Nevertheless, the relapse rate was stable throughout the study period and patients that entered the study before 2006 had an overall relapse rate of 40% vs 42% for those that were enrolled after this date. Finally, we were not able to calculate and compare cumulative glucocorticoid dose in each group, as treatment data were not collected for all patients, after occurrence of relapse. This point is important as it has been shown that part of the long-term metabolic and cardiovascular toxicity of immunosuppression is due to excessive cumulative doses of glucocorticoids, given either as a preventive remission maintenance therapy or as curative induction treatment during repeated flares of AAV [24].

In conclusion, we suggest that at least some of the patients that have reached remission of AAV require long-term immunosuppressive therapy to prevent recurrence of the disease. The challenge of future studies will be to define the best immunosuppressive scheme, providing both efficacy and limited toxicity, but also to find clinical or biological markers that will identify high-risk patients who will require prolonged therapy.

FIGURE LEGENDS

Figure 1:
Flow diagram of the REMAIN study, summarizing enrolment, intervention allocation, follow-up and data analysis.

Figure 2:
Kaplan-Meier analysis of the study population, showing relapse-free survival according to treatment group (2a), major relapse-free survival according to treatment group (2b) and relapse-free survival according to positivity or negativity of ANCA at randomization (2c). Daily dose of prednisolone and azathioprine in each group is shown above.

Supplementary figures :

Suppl. Figure1:
Median and mean doses of azathioprine at each time-point for patients of the withdrawal group (1a) and the continuation group (1b).

Suppl. Figure 2:
ANCA positivity (2a) and vasculitis damage index - VDI (2b) during follow-up according to treatment arm.

Suppl. Figure 3:
Survival without relapse according to treatment arm ,in patients with MPO-ANCA (3a) or PR3-ANCA (3b)

Suppl. Figure 4:
Survival without relapse according to treatment arm, in patients with positive (4a) or negative ANCA serology (4b) at randomization

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COMPETING INTERESTS

-Alexandre Karras has received lecture fees from Roche/Genentech
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CONTRIBUTORSHIP

AK contributed to data collection, data analysis and interpretation, manuscript preparation and review.
CP contributed to data generation, collection, analysis and interpretation, manuscript preparation and review.
MH contributed to study design and set-up, data generation, analysis and interpretation, manuscript preparation and review.
KdG contributed to data generation, analysis and interpretation, manuscript preparation and review.
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JWCT contributed to data generation, analysis and interpretation, manuscript preparation and review.
MS contributed to study design and set-up, data generation, analysis and interpretation, manuscript preparation and review.
LG contributed to data generation, analysis and interpretation, manuscript preparation and review.
DJ contributed to study design and set-up, data generation and collection, analysis and interpretation, manuscript preparation and review.

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DATA SHARING
All study data are included in this manuscript.

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