Randomized Trial of C5aR Inhibitor Avacopan in ANCA-Associated Vasculitis

David R.W. Jayne, F.R.C.P., Annette N. Bruchfeld, M.D., Lorraine Harper, M.D., Matthias Schaier, M.D., Michael C. Venning, M.D., Patrick Hamilton, M.D., Volker Burst, M.D., Franziska Grundmann, M.D., Michel Jadoul, M.D., István Szombati, M.D., Vladimír Tesař, M.D., Mårten Segelmark, M.D., Antonia Potarca, M.Sc., Thomas J. Schall, Ph.D. and Pirow Bekker, M.B.Ch.B. for the CLEAR Study Group*.

From Department of Medicine, Addenbrooke's Hospital, Vasculitis and Lupus Clinic, Box 57, Addenbrooke's Hospital, Cambridge CB2 2QQ, UK (David Jayne); Karolinska Institute, Dept of Renal Medicine, M99 Karolinska University Hospital Huddinge S-141 86 Stockholm, Sweden (Annette Bruchfeld); Institute of Clinical Sciences, Centre for Translational Inflammation Research, University of Birmingham Research Laboratories, Queen Elizabeth Hospital Birmingham, Mindelsohn Way, Edgbaston, Birmingham, B15 2WB, United Kingdom (Lorraine Harper); Renal Centre, Heidelberg, Im Neuenheimer Feld 162, D 69120 Heidelberg, Germany (Matthias Schaier); Department of Renal Medicine, Manchester Royal Infirmary Oxford Road, Manchester M13 9WL, United Kingdom (Michael Venning and Patrick Hamilton); Clinic II for Internal Medicine: Nephrology, Rheumatology, Diabetology and General Internal Medicine, Uniklinik Cologne, Kerpenerstr. 62, 50937 Cologne, Germany (Volker Burst and Franziska Grundmann); Cliniques universitaires Saint-Luc, Université catholique de Louvain, Avenue Hippocrate 10, 1200, Brussels, Belgium (Michel Jadoul); Budai Irgalmasrendi Korhaz, Frankel Leó utca 54, 1023, Budapest, Hungary (Istvan Szombati); Charles University, Ovocný trh 3-5, 116 36 Prague, Czech Republic (Vladimir Tesar); Linköping University, 581 83 Linköping,

Sweden (Mårten Segelmark); and ChemoCentryx, Inc., 850 Maude Avenue, Mountain View, CA

94043, United States (Antonia Potarca, Thomas Schall, and Pirow Bekker)

* See Supplemental Material for a list of CLEAR Study Investigators.

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Corresponding author:

David RW Jayne, F.R.C.P.

Department of Medicine

Addenbrooke's Hospital

Vasculitis and Lupus Clinic

Box 57, Addenbrooke's Hospital

Cambridge   CB2 2QQ, UK

Tel: +44 (0) 1223 586796

Fax: +44 (0) 1223 586796

email: dj106@cam.ac.uk

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Abstract

Background

Alternative complement activation is involved in the pathogenesis of anti-neutrophil cytoplasm antibody-associated vasculitis. Glucocorticoids contribute to the morbidity and mortality of vasculitis. The aim was to determine if avacopan (CCX168), an orally-administered, selective C5a receptor inhibitor, could replace oral glucocorticoids without compromising efficacy.

Methods

In this randomized, placebo-controlled trial, adults with newly-diagnosed or relapsing vasculitis received placebo plus prednisone starting at 60 mg daily (control group), avacopan 30 mg twice daily plus reduced dose prednisone, 20 mg daily, or avacopan 30 mg twice daily without prednisone. All patients received either cyclophosphamide or rituximab. The primary efficacy measure was the proportion of patients achieving a reduction in Birmingham Vasculitis Activity Score by week 12 of at least 50% and no worsening in any body system.

Results

We enrolled 67 patients, 23 in control, and 22 in each of the avacopan groups. Clinical response at week 12 was achieved in 14 of 20 (70.0%) patients in control, 19 of 22 (86.4%) in avacopan plus reduced dose prednisone group (difference from control 16.4%; two-sided 90% confidence limit -4.3, 37.1%, p=0.002 for non-inferiority), and 17 of 22 (81.0%) in avacopan without prednisone group (difference from control 11.0%; two-sided 90% confidence limit -11.0, 32.9%, p=0.01 for non-inferiority). Adverse events occurred in 21 of 23 (92%) patients in control versus 19 of 22 (86%) patients in the first avacopan, and 21 of 22 (96%) patients in the second avacopan group.

Conclusions

C5aR inhibition with avacopan was effective in replacing high dose glucocorticoids in treating

vasculitis.

Introduction

Anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV) is a serious, often life-threatening disease linked to auto-antibodies to proteinase 3 (PR3-ANCA) and myeloperoxidase (MPO-ANCA). Despite the current standard treatment with high dose glucocorticoids and either cyclophosphamide or rituximab, patients have a nine-fold increased mortality risk in the first year compared to healthy controls, attributed to infection, vasculitis activity, and renal disease.[1] Current therapies, rather than the underlying disease itself, contribute more than half of this increased risk.[2] Fifteen to 38 percent of patients develop end-stage renal disease within 5 years.[3-7] Glucocorticoids are associated with increased infection risk[8-10] and progressive organ damage.[11]

Complement 5a (C5a) and C5a receptor (C5aR, or CD88) play a central role in the pathogenesis of AAV.[12-14] C5a can prime and activate neutrophils[15] which release C5a when stimulated by inflammatory cytokines such as TNFα.[16] C5a, acting on C5aR, is a potent neutrophil chemoattractant and agonist[17] and can decrease neutrophil deformability, slowing their ability to traverse small blood vessels, particularly in the presence of ANCA.[18] C5a also activates vascular endothelial cells, promoting their retraction and increased vascular permeability.[19,20]

Avacopan, previously called CCX168, is an orally administered small-molecule C5aR antagonist that blocks the effects of C5a[21], and prevented the development of glomerulonephritis induced by anti-myeloperoxidase antibodies in a murine model of AAV.[22] We therefore tested the efficacy and safety of avacopan in patients with active AAV, treated concomitantly with cyclophosphamide or rituximab.

Results

The study ran from 12 October 2011 (first patient enrolled) until 18 January 2016. Patient disposition is shown in Figure 1. The demographics and baseline characteristics were statistically similar among the three groups (no p-values < 0.05 for comparisons across groups), except for high baseline serum creatinine on BVAS, with 15 of 23 subjects in the control group compared to 6 of 22 in the avacopan plus no prednisone group (Table 1).

Treatment responses occurred in 86% and 81% of the avacopan with reduced dose, and avacopan with no prednisone groups, respectively, and in 70% in the high dose glucocorticoid (control) group. Both avacopan groups met non-inferiority criteria (p = 0.002 for avacopan with reduced dose prednisone vs. control and p = 0.01 for avacopan with no prednisone vs. control; Table 2). The avacopan treatment response was observed across subgroups (Supplemental Table 2), and individual patient Birmingham Vasculitis Activity Score (BVAS) data showed a more consistent response in the two avacopan groups compared to control (Figure 2A); p = 0.04 at week 4 and p = 0.09 at week 12 for all avacopan compared to prednisone control. Remission (BVAS 0) at week 4 that was sustained to week 12 occurred in 9 of 43 (21%) patients on avacopan compared to 1 of 20 (5%) in the control group (Figure 2A and Table 2); p = 0.10 for all avacopan compared to prednisone control and p = 0.04 for avacopan with no prednisone compared to prednisone control. Secondary end point results are summarized in Figures 2B to 2G, and in Table 2. The mean percent decrease in BVAS at week 4 in the avacopan groups was comparable to the control group change at week 12. The mean increase in vasculitis damage index (VDI) between entry and week 12 was 0.3 and 0.2 in the two avacopan groups, respectively, compared to 0.7 in the control group (not statistically different).

Albuminuria improved early in both avacopan groups and the improvements were statistically greater than control at week 4 for both avacopan groups, and in the avacopan with reduced prednisone group vs. control group at week 12 (Table 2). Estimated glomerular filtration rate (eGFR) and hematuria improved similarly across all three groups. Urinary creatinine-corrected monocyte chemoattractant protein-1 (MCP-1), improved more in the avacopan compared to the control group at week 4 and 12, and C-reactive protein levels decreased similarly across groups (Table 2).

Health-related quality of life, including physical and mental components, improved more with avacopan compared to control based on the Medical Outcomes Survey Short Form-36 (SF-36) and EuroQOL-5D-5L (EQ-5D-5L) instruments (Table 2 and Supplemental Table 3).

Three patients received rescue glucocorticoids during the treatment period, one in the control group and two in the avacopan without prednisone group.

At the end of the 12-week treatment period, 3, 3, and 2 patients in the control, avacopan plus reduced dose prednisone, and avacopan without prednisone groups, respectively, were ANCA-negative.

The control and avacopan plus reduced prednisone groups continued to receive prednisone for the first 8 and 2 weeks, respectively, of the 12-week follow-up period, whereas the avacopan without prednisone group received no prednisone (Supplemental Table 1). Sixteen of 20 (80%), 17 of 22 (77%), and 15 of 21 (71%) patients in the control, avacopan plus reduced dose prednisone, and avacopan without prednisone groups, respectively, had a BVAS decrease of at least 50% at week 24. The BVAS mean change at week 24 was -83, -87, and -85 percent, respectively. eGFR at week 24 was 54, 59, and 55 mL/min/1.73 m^2, respectively. The UACR mean change at week 24

was -48%, -61%, and -30%, respectively. At the end of the 12-week follow-up period, 2, 5, and 6 patients, respectively, were ANCA-negative.

The incidence of all adverse events and Grade 3 or greater adverse events was similar across groups (Table 3). There were no deaths during the study. Adverse events were consistent with the underlying medical conditions and concomitant therapies. Four of 23 (17%) patients in the control group and 11 of 44 (25%) patients receiving avacopan had serious adverse events. When all adverse events are taken into account, 2, 1, and 3 patients in the control, avacopan plus reduced dose prednisone group, and avacopan without prednisone groups, respectively, reported vasculitis (worsening): two of relapse of renal vasculitis in the control group, one of vasculitis worsening in the avacopan plus low dose prednisone group, and three of relapse of microscopic polyangiitis, flare of joint vasculitis, and relapse of renal vasculitis, respectively, in the avacopan plus no prednisone group. One patient in each group had a serious infection: pneumonia, febrile infection (no source identified), and respiratory infection in the control, avacopan plus reduced dose prednisone group, and avacopan without prednisone groups, respectively. No events of sepsis were reported. One patient, in the avacopan without prednisone group, with a medical history of alcohol abuse and concomitant treatment with cyclophosphamide, co-trimoxazole, and pantoprazole had hepatic and pancreatic enzyme elevations. Study drug was discontinued in this patient, who recovered. Another patient in this group had worsening of a pre-existing skin rash.

There was a lower incidence of adverse effects potentially related to glucocorticoid use in patients receiving avacopan, 15 of 44 (34%), compared to control, 15 of 23 (65%); p = 0.02. This difference was primarily driven by a lower incidence of psychiatric disorders and new-onset or worsening diabetes (Table 3).

More patients in the avacopan without prednisone group, but not the avacopan plus reduced dose prednisone group, had Grade 2 or 3 lymphopenia during the 12-week treatment period compared to control (Table 3). One patient in the avacopan plus reduced dose prednisone group had an increase in creatine phosphokinase. This was not accompanied by any signs or symptoms of muscle injury, and the values returned to normal with uninterrupted avacopan treatment. Treatment was stopped in the patient with elevated liver and pancreatic enzymes (in the avacopan without prednisone group), who also had an elevated bilirubin level, which recovered.

Discussion

High dose glucocorticoids have for half a century been considered as indispensable in the treatment of AAV, despite their well-documented toxicities.[23,2,8-11] In this study we show that inhibition of the C5a receptor may be an alternative to use of oral glucocorticoids, and that C5a is an important inflammatory mediator in AAV.

Vasculitis activity is inadequately controlled in many patients. In a clinical trial comparing rituximab and cyclophosphamide, the primary outcome measure of disease remission at 6 months was not achieved in 42% of patients[24], due to disease flares (36%), uncontrolled disease, discontinuation due to adverse events, or inability to completely taper glucocorticoids.[25]

This clinical trial met its primary end point indicating that the orally administered C5aR inhibitor avacopan can replace high dose glucocorticoids effectively and safely in patients with AAV. Several lines of evidence suggest that avacopan might also add benefit. In addition to avoiding glucocorticoid side effects, individual patient BVAS data suggest a rapid, consistent clinical response in patients receiving avacopan. Early efficacy with avacopan was further substantiated by a rapid improvement in albuminuria, which is common in patients with AAV and is a prognostic factor for poor renal outcome.[26,27] Therefore, the avacopan benefit on albuminuria may translate into improved preservation of renal function. Results from the 12-week follow-up period indicate that there was no immediate rebound effect following withdrawal of avacopan treatment.

A high level of the renal inflammation marker, urinary monocyte chemoattractant protein-1, also correlates with poorer outcomes in patients with active renal vasculitis and other renal diseases.[28-31] Base line urinary MCP-1:creatinine ratio was 3- to 5-fold higher than the upper limit

of the reference range for healthy subjects[32] and renal inflammation improved rapidly and to a greater extent with avacopan compared to control, which may lead to less glomerular and renal tubular damage. eGFR and hematuria improved similarly in all three groups over the 12-week treatment period, indicating that improvement in renal function in patients receiving avacopan did not require high dose glucocorticoids.

Patients with AAV may present with symptoms such as fatigue, fever, headache, arthralgia, and myalgia, which negatively impact quality of life. Results showed that avacopan broadly improved various aspects of patients' well-being, albeit from a small sample of patients. This may translate into less work absenteeism, fewer visits to the doctor, and ultimately reduced health care cost.

Avacopan appeared to be well tolerated and safe in this trial. There was a lower incidence of adverse effects related to glucocorticoid use, such as new onset diabetes, psychiatric disorders, weight gain, fracture, and cataract in the avacopan treatment groups compared to control, indicating that using avacopan instead of glucocorticoids may avoid these side effects. Curiously, lymphopenia was observed more commonly in the avacopan without prednisone group, but not the avacopan plus reduced dose prednisone group, compared to control. This argues against a detrimental avacopan effect. A more plausible explanation is that the absence of prednisone in the avacopan without prednisone group is unmasking the known lymphopenic effect of cyclophosphamide and rituximab, because in the short term, glucocorticoids cause an increase in lymphocyte count.[33]

The study has limitations. It is relatively small and the treatment duration was short. The 12-week treatment period was driven by the available toxicology data at the time of study launch. By necessity, the trial was performed in three sequential steps, rather than as a concurrent, parallel

group trial, since glucocorticoids could not be replaced completely without having some evidence of the efficacy of avacopan. A relatively small number of patients received rituximab rather than cyclophosphamide concomitant treatment; rituximab was not yet approved at the time of study launch. Treatment response instead of remission based on BVAS was used as the primary end point in this study because of the short treatment duration. There is precedence for using such a response (or partial remission) endpoint based on BVAS[34,35]. The glucocorticoid tapering schedule is relatively rapid compared to the RAVE study[24], but is consistent with the RITUXVAS study conducted in Europe at the same time[36]. There is no consensus glucocorticoid tapering schedule in AAV, and the current EULAR/ERA-EDTA guidance is to taper glucocorticoids more rapidly (7.5 to 10 mg prednisone by 3 months) to avoid side effects[37]. Since this was the first study with avacopan in AAV, patients with severe end-organ manifestations needed to be excluded; this may limit the generalizability of the findings.

Based on the very promising results from this study, avacopan development was advanced to Phase 3.

Concise Methods

Study design and patients

We performed a randomized, double-blind, placebo-controlled trial at 32 centers in Europe. The aim was to reduce or replace glucocorticoid treatment with avacopan without compromising efficacy in treating AAV. Since there were no available data prior to the study regarding the ability of avacopan to safely replace glucocorticoids, the original primary objective of the study was to assess the safety of avacopan. Therefore, the study was done in a stepwise manner with three sequential steps. In step 1, we tested whether avacopan permitted a reduced oral prednisone dose. If there were no unexpected serious adverse events or an excess of glucocorticoid rescue events, step 2 would be performed. In step 2, we tested whether avacopan could replace oral prednisone entirely. If successful, step 3 would follow, which was to be an expansion of the study size. After successful completion of the first two steps, an efficacy endpoint based on treatment response was added. Twelve weeks treatment with avacopan was followed by 12 weeks without study drug. The prednisone tapering schedule is shown in Supplemental Table 1.

The inclusion and exclusion criteria are provided in the Supplement.

The trial was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Ethics committees and institutional review boards approved the research protocol. All patients gave written informed consent before entry.

Randomization and Treatment

After screening, patients were stratified based on having newly diagnosed or relapsing disease (all three steps), and by PR3 or MPO-ANCA, and cyclophosphamide or rituximab treatment (step

3). In step 1, 12 patients were enrolled and randomly assigned in a 2 to 1 ratio to receive 30 mg avacopan twice daily plus 20 mg prednisone, or placebo avacopan plus 60 mg prednisone. In step 2, 14 patients were enrolled and randomly assigned in a 2 to 1 ratio to receive 30 mg avacopan twice daily without prednisone or placebo avacopan plus 60 mg prednisone. All patients in steps 1 and 2 received cyclophosphamide intravenously at 15 mg/kg up to 1.2 g on day 1 and weeks 2, 4, 8, and 12, followed by oral azathioprine at a target dose of 2 mg/kg/day from week 14 to 24. Rituximab was not allowed in steps 1 and 2, because it was not approved at the time of study launch. The cyclophosphamide dose was adjusted based on age, eGFR, and white blood cell (WBC) count (see Supplement). In step 3, 41 patients were randomly assigned (1:1:1) to receive 30 mg avacopan twice daily plus 20 mg prednisone, 30 mg avacopan twice daily plus placebo prednisone, or placebo avacopan plus 60 mg prednisone. All patients in step 3 received either cyclophosphamide followed by azathioprine as described above, or intravenous rituximab 375 mg/m^2/week for 4 weeks.

Stratification and randomization were performed centrally via an interactive voice response system using a minimization algorithm to maintain balance among the treatment groups with respect to strata and study center.[38]

Patients and all study personnel were masked to treatment allocation. All study drugs had matching active and placebo capsules, identical bottles and boxes.

Study assessments are provided in the Supplement.

End points

The primary efficacy end point was the proportion of patients with a treatment response at week 12 defined as a BVAS decrease from base line of at least 50 percent plus no worsening in any body system. Patients receiving rescue glucocorticoids were considered non-responders. Secondary endpoints included the proportion of patients with a renal response, defined as an improvement in eGFR calculated using the Modified Diet in Renal Disease equation (see supplement), hematuria, and albuminuria at week 12, the proportion of patients with disease remission (BVAS 0), change from baseline in BVAS, eGFR, urinary albumin:creatinine ratio (UACR), urinary red blood cell count, urinary monocyte chemoattractant protein-1 (MCP-1):creatinine ratio, VDI, SF-36 version 2, EQ-5D-5L, and rescue glucocorticoid use. The week 24 follow-up data were summarized.

Statistical analysis

The planned study size was 60 patients. This study size was based on feasibility given that AAV is an orphan disease. Efficacy analyses were conducted on the intention-to-treat (ITT) population defined as all patients with at least one post base line on-treatment BVAS assessment. The safety population included all randomized patients who received at least one dose of study drug.

For the primary efficacy end point, the proportion of patients achieving disease response was calculated for the comparison between each avacopan group against control. If the lower bound of the 1-sided 95% confidence interval for the difference (avacopan minus control) was greater than -0.20, the respective avacopan group would be considered not inferior to control. A 20 percent non-inferiority boundary and a 1-sided 95% confidence interval were considered appropriate in the context of a relatively small Phase 2 clinical trial in an orphan disease setting. There is also precedent for selecting a 20 percent non-inferiority boundary in AAV[24]. If the

lower bound was greater than 0.0, the respective avacopan group would be considered superior to control. As pre-specified, results from all three study steps were combined for the primary analysis.

Continuous variables were analyzed using a mixed effects model for repeated measures with treatment group, study visit, treatment-by-visit interaction, and randomization strata as factors, and base line as covariate. Patients were considered as repeated measure units over visits. Data that were not normally distributed, e.g., UACR, were log-transformed before analysis.

The study was registered with ClinicalTrials.gov (NCT01363388).

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Statement of Competing Financial Interests

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Figure Legends

Figure 1. Patient Disposition. Of 87 patients screened, 67 were enrolled. The main reasons for study exclusion were insufficient disease activity, low white blood cell count, and severe disease activity. BVAS = Birmingham Vasculitis Activity Score, ANCA = anti-neutrophil cytoplasm antibody, eGFR = estimated glomerular filtration rate, PT = prothrombin time, PTT = partial thromboplastin time, AE = adverse event.

Figure 2. Efficacy Profile of Avacopan. (A) Birmingham Vasculitis Activity Score percent change from base line for each patient, presented by treatment group; (B) Birmingham Vasculitis Activity Score mean ± SEM percent change from base line for placebo plus high dose prednisone, n = 20 (♦), avacopan plus reduced dose prednisone, n = 22 (■), and avacopan without prednisone, n = 21 (▲); (C) First morning urinary albumin to creatinine ratio percent change from base line, calculated as 100 X (geometric mean at the study visit) / (geometric mean at base line) for placebo plus high dose prednisone, n = 20 (♦), avacopan plus reduced dose prednisone, n = 22 (■), and avacopan without prednisone, n = 20 (▲); * $P < 0.05$, ** $P < 0.01$, and *** $P < 0.001$ for avacopan compared to control by mixed effects model for repeated measures analysis with treatment group, study visit, treatment-by-visit interaction, and randomization strata as factors, and base line as covariate. (D) First morning urinary monocyte chemoattractant protein-1 to creatinine ratio percent change from base line, calculated as 100 X (geometric mean at the study visit) / (geometric mean at base line) for placebo plus high dose prednisone, n = 20 (♦), avacopan plus reduced dose prednisone, n = 22 (■), and avacopan without prednisone, n = 21 (▲); ** $P < 0.01$, and *** $P < 0.001$ for avacopan compared to control by mixed effects model for repeated measures analysis with treatment group, study visit, treatment-by-visit interaction, and randomization strata as factors, and base line as covariate. (E)

and (F) Health-related Quality of Life measurement Medical Outcomes Study Short Form-36

version 2 Physical Functioning and Role Emotional components, respectively, expressed as mean

± SEM over the course of the treatment period for placebo plus high dose prednisone, n = 10 (♦),

avacopan plus reduced dose prednisone, n = 14 (■), and avacopan without prednisone, n = 9 (▲);

the scale ranges from 0 to 100, from low to high functioning; * $P < 0.05$ for avacopan compared

to control regarding change or percent change from base line by mixed effects model for repeated

measures analysis with treatment group, study visit, treatment-by-visit interaction, and

randomization strata as factors, and base line as covariate. (G) Health-related Quality of Life

measurement EuroQOL-5D-5L visual analogue scale expressed as mean ± SEM for placebo plus

high dose prednisone, n = 10 (♦), avacopan plus reduced dose prednisone, n = 14 (■), and

avacopan without prednisone, n = 9 (▲); the scale is measured from 0 to 100, from low to high

self-perception of health status; * $P < 0.05$ for avacopan compared to control regarding change

from base line by mixed effects model for repeated measures analysis with treatment group, study

visit, treatment-by-visit interaction, and randomization strata as factors, and base line as

covariate.

Table 1. Demographics and Baseline Characteristics*

Category	Placebo plus 60 mg prednisone control (N=23)	Avacopan plus 20 mg prednisone (N=22)	Avacopan without prednisone (N=22)
Age (years)	59.1±14.0	57.0±14.2	57.4±14.0
Sex, Male/Female—no.	17/6	14/8	16/6
Race, White—no.	23	22	22
Duration of vasculitis (months)	0 (0-162)	0 (0-61)	1 (0-108)
Body mass index (kg/m^2)	27.3±7.1	24.9±4.0	26.5±4.7
Disease history			
Newly Diagnosed—no. (%)	18 (78)	15 (68)	16 (73)
Relapsed Disease—no. (%)	5 (22)	7 (32)	6 (27)
ANCA type			
Anti-myeloperoxidase positive—no. (%)	10 (43)	12 (55)	13 (59)
Anti-proteinase 3 positive—no. (%)	11 (48)	10 (45)	8 (36)
Both anti-myeloperoxidase and anti-proteinase 3 positive—no. (%)	1 (4)	0	0
ANCA equivocal or negative—no. (%)	1 (4%)	0	1 (5%)
Disease type			
Granulomatosis with polyangiitis—no. (%)	10 (44)	11 (50)	12 (55)

Category	Placebo plus 60 mg prednisone control (N=23)	Avacopan plus 20 mg prednisone (N=22)	Avacopan without prednisone (N=22)
Microscopic polyangiitis—no. (%)	12 (52)	11 (50)	10 (45)
Unknown—no. (%)	1 (4)	0	0
Disease assessment scores			
Birmingham Vasculitis Activity Score†	13.2±5.8	14.3±6.0	13.8±6.4
Vasculitis Damage Index	1.2±1.4	0.9±1.5	0.5±1.2
Organ involvement			
Renal involvement—no. (%)	23 (100)	21 (95)	21 (95)
Rise in serum creatinine—no. (%)	2 (9)	0	0
High serum creatinine—no. (%)	15 (65)	11 (50)	6 (27) ‖
Hematuria—no. (%)	22 (96)	20 (91)	21 (95)
Proteinuria—no. (%)	18 (78)	20 (91)	16 (73)
Hypertension—no. (%)	3 (13)	5 (23)	2 (9)
Pulmonary involvement—no. (%)	9 (39)	8 (36)	7 (32)
Constitutional signs or symptoms‡—no. (%)	19 (83)	17 (77)	16 (73)
Cutaneous involvement—no. (%)	4 (17)	1 (5)	4 (18)
Mucous membranes and eyes—no. (%)	1 (4)	1 (5)	4 (18)
Ear, nose, and throat—no. (%)	9 (39)	5 (23)	8 (36)
Cardiovascular involvement—no. (%)	0	1 (5)	2 (9)
Neurological involvement—no. (%)	3 (13)	5 (23)	2 (9)

Category	Placebo plus 60 mg prednisone control (N=23)	Avacopan plus 20 mg prednisone (N=22)	Avacopan without prednisone (N=22)
Estimated glomerular filtration rate (mL/min/1.73 m^2)§	47.6±15.1	52.5±26.7	54.7±19.6
Urinary albumin:creatinine ratio (mg/g)¶	354 (28-5962)	279 (24-2459)	283 (25-3051)
Prior medications of interest			
Systemic glucocorticoids—no. (%)	11 (48)	14 (64)	11 (50)
Prednisone-equivalent daily dose per patient (mg)	53	49	44
IV glucocorticoids—no. (%)	5 (25)	9 (41)	5 (23)
Immunosuppressants including azathioprine, methotrexate, or mycophenolate mofetil—no. (%)	2 (9)	4 (18)	3 (14)
Cyclophosphamide or rituximab—no.	0	0	0

* Plus-minus values are mean±SD

† The Birmingham Vasculitis Activity Score version 3 was used to capture vasculitis disease activity. The score ranges from 0 to 63 with higher scores denoting more severe disease activity.

‡ Constitutional signs and symptoms included weight loss, fever, arthralgia, and myalgia.

§ Estimated glomerular filtration rate based on Modified Diet in Renal Disease equation derived from serum creatinine (see supplement).

¶ Urinary albumin:creatinine ratio values are geometric means and ranges.

‖ $p < 0.05$ for comparison of avacopan vs. control; Fisher's exact test.

Table 2. Efficacy Results for 12-Week Treatment Period*

	Placebo plus 60 mg prednisone control (N=20)		Avacopan plus 20 mg prednisone (N=22)		Avacopan without prednisone (N=21)	
Birmingham Vasculitis Activity Score and Vasculitis Damage Index end points						
Primary endpoint: Treatment response† at week 12—no. (%)	14 (70.0)		19 (86.4)		17 (81.0)	
Difference in percentage compared to control	--		16.4		11.0	
Two-sided 90% confidence interval for difference in percentage, avacopan minus control	--		-4.3, 37.1		-11.0, 32.9	
Birmingham Vasculitis Activity Score	Actual	%Change	Actual	%Change	Actual	%Change
Base line	13.6±1.4	--	14.3±1.3	--	13.6±1.4	--
Week 4	6.6±1.2	-40±12	4.9±0.7	-64±5	5.3±1.3	-61±9
Week 12	5.0±1.6	-56±14	2.6±0.7	-79±5	3.6±1.1	-73±7
Vasculitis Damage Index	Actual	Change	Actual	Change	Actual	Change
Base line	1.2±0.3	--	0.9±0.3	--	0.5±0.3	--
Week 12	1.8±0.4	0.7±0.2	1.2±0.3	0.3±0.1	0.8±0.3	0.2±0.1
Remission (BVAS 0) at week 12—no. (%)	8 (40)		10 (45)		7 (33)	
Remission at week 4 sustained through week 12—no. (%)	1 (5)		3 (14)		6 (29)‖	
Renal end points						
	N=20		N=18		N=18	
Renal response‡ at week 12—no. (%)	8 (40)		10 (56)		6 (33)	

	Placebo plus 60 mg prednisone control (N=20)		Avacopan plus 20 mg prednisone (N=22)		Avacopan without prednisone (N=21)	
Urinary albumin:creatinine ratio (milligram per gram creatinine) in patients with albuminuria at base line	N=20		N=22		N=20	
	Actual	%Change	Actual	%Change	Actual	%Change
Base line	318	--	279	--	280	--
Week 4	355	15	168	-40§	142	-47¶
Week 12	252	-21	127	-56§	158	-43
Estimated glomerular filtration rate (milliliter per minute per 1.73 square meters	Actual	Change	Actual	Change	Actual	Change
Base line	47.2±3.5	--	52.5±5.7	--	54.8±4.4	--
Week 4	45.8±3.1	-0.8±2.0	54.5±4.5	2.0±2.3	53.5±4.8	-1.2±3.7
Week 12	52.8±3.6	5.6±2.3	56.2±4.3	6.0±2.3	56.1±5.2	0.8±2.2
Urinary red blood cell count (cells per high power field) in patients with hematuria at base line	N=20		N=20		N=19	
	Actual	%Change	Actual	%Change	Actual	%Change
Base line	22	--	26	--	17	--
Week 4	5	-76	7	-72	6	-65
Week 12	2	-92	5	-83	3	-85
Inflammation markers						
Urinary monocyte chemoattractant protein-1:creatinine (picogram per milligram)	Actual	%Change	Actual	%Change	Actual	%Change

	Placebo plus 60 mg prednisone control (N=20)		Avacopan plus 20 mg prednisone (N=22)		Avacopan without prednisone (N=21)	
Base line	752	--	1266	--	806	--
Week 4	641	-15	588	-54§	557	-30
Week 12	426	-43	373	-70¶	374	-50
C-reactive protein (milligram per liter)	Actual	%Change	Actual	%Change	Actual	%Change
Base line	9.3	--	5.9	--	5.0	--
Week 4	2.1	-76	1.9	-68	4.0	-17‖
Week 12	3.6	-61	1.3	-77	2.7	-41
Health-related quality of life endpoints						
	N=10		N=14		N=9	
Short Form-36 version 2 Physical Functioning	Actual	%Change	Actual	%Change	Actual	%Change
Base line	67±7	--	68±8	--	74±11	--
Week 4	71±5	31±30	75±6	61±51	90±6	68±71‖
Week 12	72±4	33±31	84±4	83±65	93±3	61±57‖
Short Form-36 version 2 Mental Health	Actual	%Change	Actual	%Change	Actual	%Change
Base line	66±5	--	62±5	--	82±7	--
Week 4	68±5	4±3	73±6	22±8	79±6	-8±8‖
Week 12	65±5	1±8	79±6	34±11¶	89±4	3±6§
EuroQOL-5D-5L visual analogue scale	Actual	%Change	Actual	%Change	Actual	%Change
Base line	69±5	--	65±5	--	69±6	--

	Placebo plus 60 mg prednisone control (N=20)		Avacopan plus 20 mg prednisone (N=22)		Avacopan without prednisone (N=21)	
Week 4	66±5	-3±5	70±5	20±15	80±4	7±7‖
Week 12	66±5	-3±6	75±5	28±14	78±4	5±2

*Plus-minus values are mean±SEM; urinary albumin:creatinine ratio, urinary red blood cell count, and urinary monocyte chemoattractant protein-1:creatinine ratio actual values are geometric means, and percentage change from base line are ratios of geometric means of visit over base line. Number of patients per group for each end point is as indicated in the first row unless otherwise indicated.

† Primary endpoint: treatment response based on Birmingham Vasculitis Activity Score decrease of at least 50% from base line and no worsening in any body system. Avacopan plus 20 mg prednisone group was statistically noninferior to control (P=0.002) and avacopan without prednisone was also noninferior to control (P=0.01)

‡Renal response was assessed in patients with hematuria and albuminuria at base line, and was defined as an improvement in renal parameters, i.e., an increase in estimated glomerular filtration rate, a decrease in urinary red blood cell count, and a decrease in urinary albumin:creatinine ratio

§ P<0.01 for comparison of avacopan vs. control

¶ P<0.001 for comparison of avacopan vs. control

‖ P<0.05 for comparison of avacopan vs. control

Table 3. Safety Results for 12-Week Treatment Period

	Placebo plus 60 mg prednisone control (N=23)	Avacopan plus 20 mg prednisone (N=22)	Avacopan without prednisone (N=22)
Patients with any adverse event—no. (%)	21 (91)	19 (86)	21 (96)
Patients with any Grade 3 or greater adverse event—no. (%)	2 (9)	2 (9)	2 (9)
Deep vein thrombosis	0	1 (5)	0
Febrile infection	0	1 (5)	0
Hepatic and pancreatic enzymes increased	0	0	1 (5)
Pneumonia	1 (4)	0	0
Renal vasculitis	1 (4)	0	0
Renal impairment	0	0	1 (5)
Patients with any serious adverse event*—no. (%)	4 (17)	3 (14)	8 (36)
Vasculitis	1 (4)	1 (5)	3 (14)
Infection	1 (4)	1 (5)	1 (5)
Back pain and vertebral fracture	1 (4)	0	0
C-reactive protein increase	0	0	1 (5)
Dehydration	1 (4)	0	0
Hematuria	0	1 (5)	0
Hepatic and pancreatic enzymes increased	0	0	1 (5)
Musculoskeletal chest pain	0	1 (5)	0

	Placebo plus 60 mg prednisone control (N=23)	Avacopan plus 20 mg prednisone (N=22)	Avacopan without prednisone (N=22)
Rash	0	0	1 (5)
Renal impairment	0	0	1 (5)
Patients with any adverse effect potentially related to glucocorticoids—no. (%)	15 (65)	4 (18)	11 (50)
Psychiatric disorders†—no. (%)	6 (26)	2 (9)	1 (5)
New-onset or worsening hypertension‡—no. (%)	5 (26)	2 (9)	8 (36)
New-onset or worsening diabetes mellitus/hyperglycemia§—no. (%)	4 (17)	0	1 (5)
Weight gain more than 10 kg—no. (%)	2 (9)	1 (5)	0
Bone fractures—no. (%)	1 (4)	0	0
Cataracts—no. (%)	1 (4)	0	0
Serious infections—no. (%)	1 (4)	1 (5)	1 (5)
Safety laboratory abnormalities¶			
Lymphopenia			
Grade 2	1 (4)	1 (5)	3 (14)
Grade 3	0	1 (5)	3 (14)
ALT increase, Grade 2	1 (4)	1 (5)	1 (5)
Bilirubin increase, Grade 3	0	0	1 (5)
Creatine phosphokinase increase, Grade 3	0	1 (5)	0

*Serious adverse events were defined as any adverse event that resulted in death, was immediately life threatening, required or prolonged hospitalization, resulted in persistent or significant disability or incapacity, was a birth defect, or was an important event that might jeopardize the patient or might have required intervention to prevent any of the above.

†All adverse events of psychosis, anxiety, amnesia, convulsions, delirium, dementia, depression, mania, emotional instability, irritability, euphoria, hallucinations, impaired cognition, increased motor activity, insomnia, memory loss, mania, mood swings, neuritis, neuropathy, paresthesia, personality changes, restlessness, schizophrenia, vertigo, or withdrawal behavior.

‡Defined as adverse events of hypertension, worsening hypertension, or high blood pressure, plus all patients with a systolic blood pressure increase of at least 20 mm Hg, and greater than 140 mm Hg (systolic), or diastolic blood pressure increase of at least 10 mm Hg, and greater than 90 mm Hg (diastolic), on at least two consecutive study visits.

§All adverse events of hyperglycemia, diabetes mellitus, increased blood glucose, plus all patients with a fasting blood glucose post baseline that is above the upper limit of normal on at least 2 consecutive study visits.

¶Grading according to Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0, published: May 28, 2009 (v4.03: June 14, 2010), U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute.
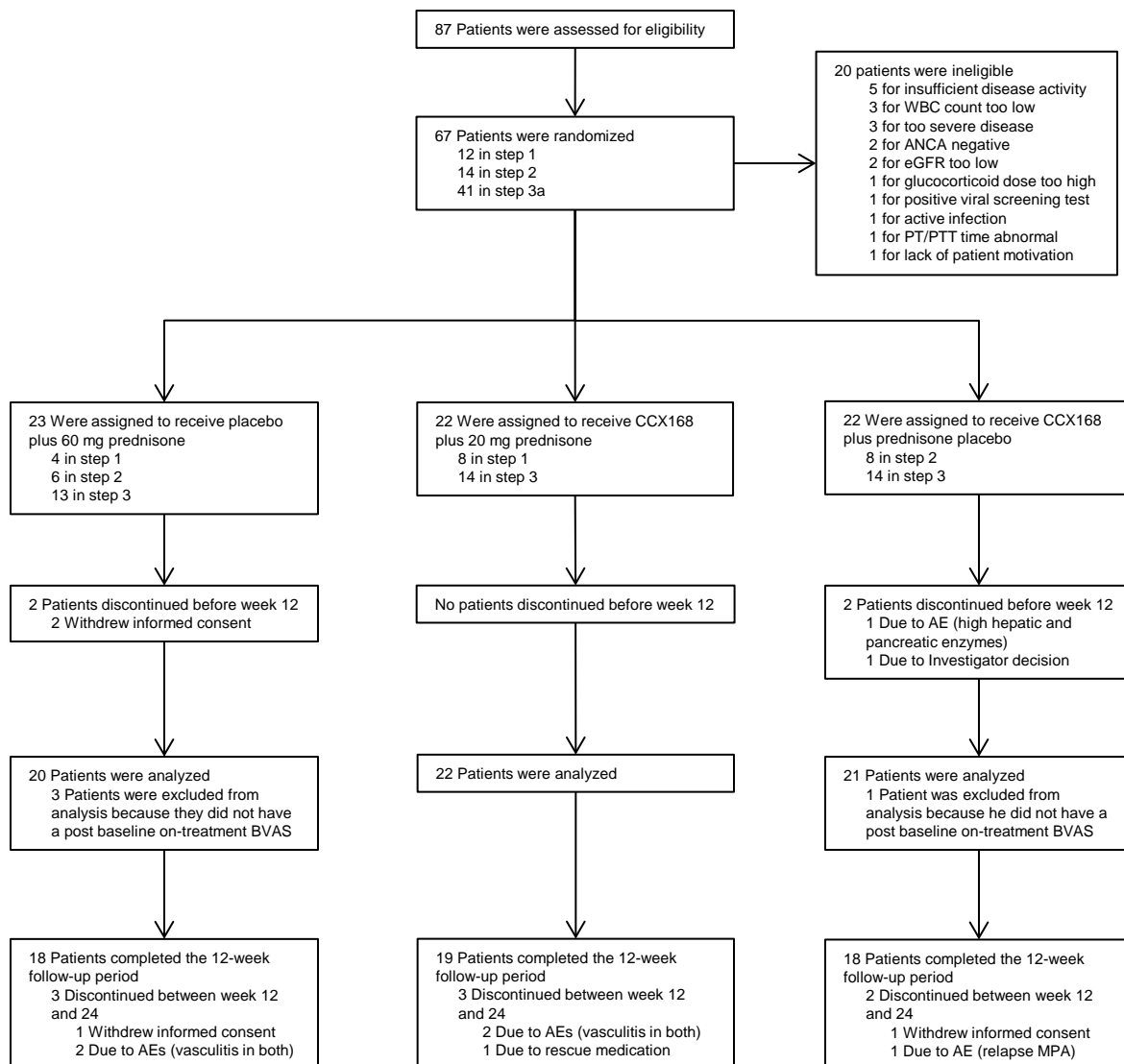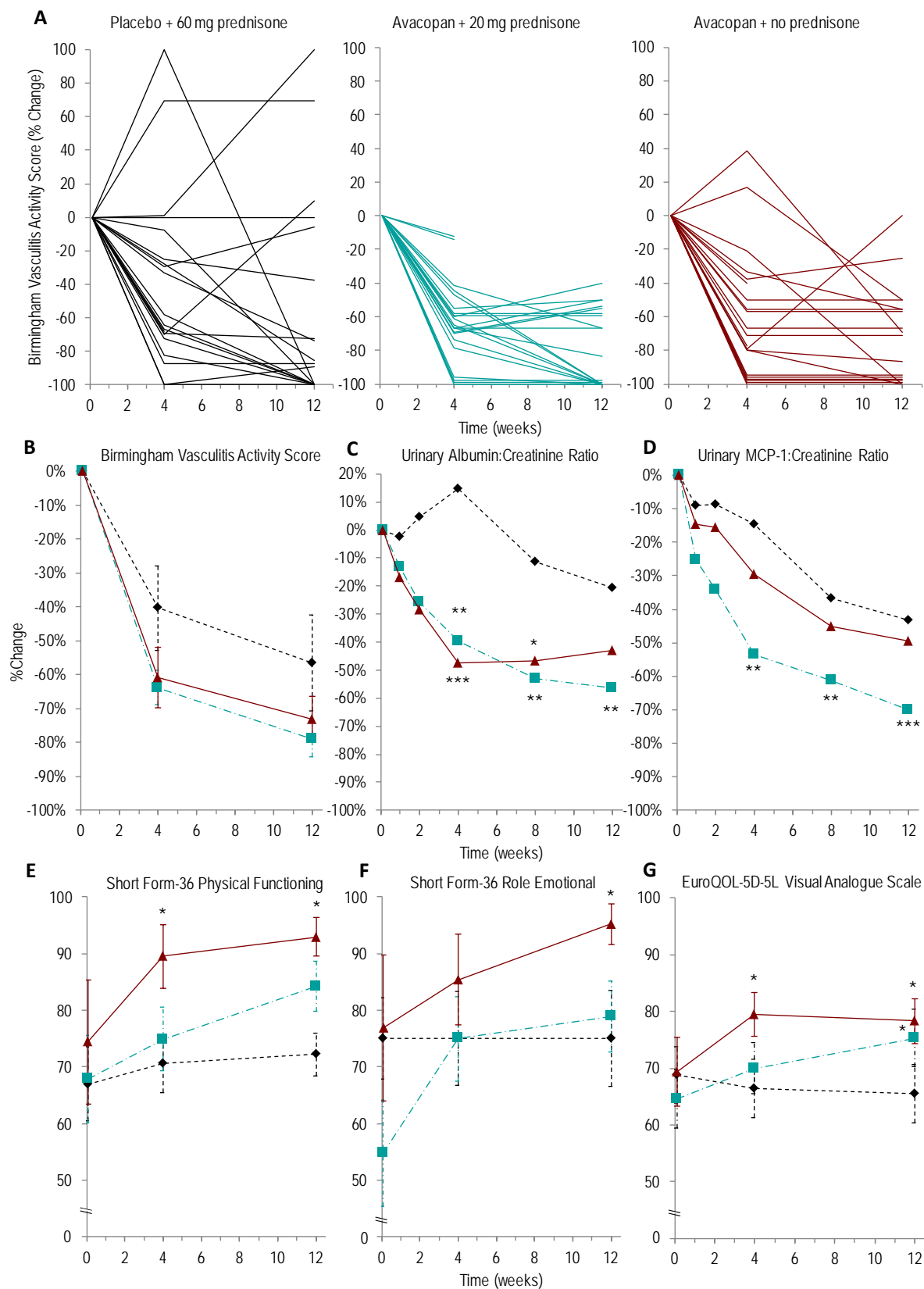
Figure 1

Figure 2

Supplemental Material

Participating investigators in CLEAR Trial:

Austria—K. Lhotta, Landeskrankenhaus Feldkirch, Feldkirch;

Belgium—M. Jadoul, Cliniques Universitaires Saint-Luc, Brussels; R. Hellemans, Antwerp University Hospital - Universitair Ziekenhuis Antwerpen, Edegem (Antwerp); P. Peeters, University Hospital Gent, Gent; J. Sennesael, University Hospital Brussels, Brussels; C. Bovy, Centre Hospitalier Universitaire de Liège, Liège; B. Sprangers, Universitair Ziekenhuis Leuven, Leuven;

Czech Republic— V.Tesar, Department of Nephrology, General University Hospital, Prague; O. Viklicky, Institute for Clinical and Experimental Medicine (IKEM), Prague;

France—C. Rigothier, CHU Bordeaux - Hospital Pellegrin, Bordeaux; L. Vrigneaud, Centre Hospitalier de Valenciennes, Valenciennes; A. Karras, Georges Pompidou European Hospital, Paris;

Germany— M. Schaier and M. Zeier, Universitaetsklinikum Heidelberg – Nephrologie, Heidelberg; H. Mehling, Charite, Experimental and Clinical Research Center (ECRC), Berlin; V. Burst and F. Grundmann, Universitaetsklinik Koeln, Cologne; C. Hugo, Universitaetsklinikum Carl Gustav Carus, Technische Universitaet, Dresden; R. Voll, University Hospital Freiburg, Freiburg;

Hungary—I. Szombati, Buda Clinic, Budapest;

The Netherlands—A. Rutgers, Universitair Medisch Centrum Groningen, Groningen; O. Bredewold, Leids Universitair Medisch Centrum, Leiden; P. Van Daele, Erasmus Medisch Centrum, Rotterdam;

Poland—K. Ciechanowski, Klinika Nefrologii, Transplantologii i Chorób Wewnetrznych, Samodzielny Publiczny Szpital Kliniczny nr 2 Pomorskiej Akademii Medycznej w Szczecinie, Szczecin;

Sweden—A. Bruchfeld, Karolinska University Hospital, Stockholm; D. Selga, Njurkliniken Lund, Skanes Universitetssjukhus, Lund; K. Westman, Skane University Hospital, Malmo; M. Segelmark, Linköping University, Linköping;

United Kingdom—D. Jayne, Addenbrooke's Hospital - Cambridge University Hospitals, Cambridge; A. Salama, Royal Free Hospital, London: L. Harper, University of Birmingham - Queen Elizabeth Hospital, Birmingham; R. Luqmani, Nuffield Orthopaedic Centre, Oxford; M. Venning and P. Hamilton, University of Manchester, Royal Infirmary, Manchester.

Study Inclusion and Exclusion Criteria

Eligible patients were at least 18 years old and had newly diagnosed or relapsing granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis according to the Chapel Hill Consensus Conference definitions[1], that required cyclophosphamide treatment (steps 1 and 2), cyclophosphamide or rituximab (step 3), were PR3 or MPO-ANCA positive or ANCA positive by indirect immunofluorescence, had an eGFR of at least 20 mL/min/1.73 m^2, had biopsy-proven renal vasculitis or hematuria (greater than 30 red blood cells per high power field or greater than 2+ by urine dipstick) plus albuminuria (at least 0.5 g/g creatinine) for steps 1 and 2, or had at least one major or three non-major items, or at least two renal items on the BVAS version 3[2] for step 3. Since the BVAS version 3 does not designate "major" items, these were selected to be consistent with the BVAS WG[3].

Patients were excluded if they had severe disease (including rapidly progressive glomerulonephritis, alveolar hemorrhage leading to grade 3 hypoxia, rapid-onset mononeuritis multiplex, or central nervous system involvement), any other autoimmune disease, coagulopathy or bleeding disorder, had received cyclophosphamide within 12 weeks, rituximab within 12 months prior to screening (or 6 months with B-cell reconstitution, CD19 count $>0.01 \times 10^9$/L), cumulative dose of intravenous glucocorticoids greater than 3 g within 12 weeks, or oral glucocorticoids of more than 10 mg per day prednisone equivalent for more than 6 weeks prior to screening.

Study Assessments

The Birmingham Vasculitis Activity Score (BVAS) version 3 was completed during screening, day 1 (base line), and weeks 4, 12, 16, and 24. The BVAS score was calculated according to the guidelines for the BVAS version 3[2]. First morning urine samples for albumin, monocyte chemoattractant protein-1 (MCP-1), and creatinine were collected at day 1 and weeks 1, 2, 4, 8, 12, 16, and 24. Urine albumin was measured by a nephelometric assay, MCP-1 by ELISA, and creatinine by a kinetic colorimetric assay in a central laboratory (Medpace Reference Laboratory, Belgium). Serum creatinine, for eGFR calculation, and urine red blood cell microscopy were performed regularly over the study course. eGFR (according to the Modified Diet in Renal Disease equation)=$175 \times$(serum creatinine, mg/dL)$^{-1.154} \times$(age, years)$^{-0.203} \times$(0.742 if female)$\times$(1.212 if black). The Medical Outcomes Study Short Form-36 version 2 (SF-36) survey and the EuroQOL-5-D-5L (EQ-5D-5L) questionnaire were completed (in step 3 only) at day 1, and weeks 4, 12, and 24. The vasculitis damage index (VDI)[4] was completed on day 1 and weeks 12 and 24.

Safety was monitored at each study visit by assessing adverse events and laboratory data. The incidence of adverse effects commonly associated with glucocorticoid use, including

psychiatric disorders, hypertension, diabetes mellitus/hyperglycemia, weight gain, bone fractures, cataracts, and serious infections was summarized. These effects were selected based on guidance from AAV experts, as well as those reported in patients with AAV[5,6]. For example, infection resulted in 50% of deaths in AAV studies[5], gastrointestinal bleeding in 5%[5]. Also diabetes mellitus (8%[5] and 11%[6]), fractures (3%[5] and 15%[6]), and cataracts (9%[6]) occur frequently. Patient compliance with taking study medication was assessed based on returned capsule counts at each study visit.

Criteria for adjusting the cyclophosphamide dose:

The cyclophosphamide dose was determined by four factors: subject age, estimated glomerular filtration rate, WBC count at the study visit, and WBC count nadir in between dose pulses (where applicable):

Age:

- If <60 years, a full dose was given (unless influenced by the other three factors);

- If 60 to 70 years, the dose was reduced by 2.5 mg/kg;

- If > 70 years, the dose was reduced by 5 mg/kg.

Estimated glomerular filtration rate:

- If ≥30 ml/min, a full dose was given (unless influenced by the other three factors);

- If <30 ml/min, the dose was reduced by 2.5 mg/kg.

WBC count at the time of cyclophosphamide dose (local lab WBC counts):

- If ≥4 x 10^9/L, a full dose was given (unless influenced by the other three factors);

- If 2 to 3.9 x 10^9/L, the dose was reduced by 25%;

- If <2 x 10^9/L, the dose was withheld until the WBC count increased to above 3 x 10^9/L.

WBC count nadir in between cyclophosphamide doses:

- If $>3 \times 10^9$/L, a full dose was given (unless influenced by the other three factors);

- If 2 to 3 $\times 10^9$/L, the dose was reduced by 20%;

- If 1 to 1.9 $\times 10^9$/L, the dose was reduced by 40%;

- If $<1 \times 10^9$/L, the next dose was withheld and further dosing was only given if the WBC was $>3 \times 10^9$/L.

Data Monitoring Committee

An independent external Data Monitoring Committee (DMC) oversaw the study and periodically reviewed safety data. The DMC advised the sponsor regarding transition between steps. At all its visits, the DMC recommended unchanged continuation of the study.

References

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Supplemental Table 1. Pre-Specified Prednisone Dose Tapering Schedule for the Three Treatment Groups

Study Week	Placebo plus 60 mg prednisone* control	Avacopan plus 20 mg prednisone	Avacopan without prednisone
1	60 mg (or 45 mg for <55 kg subjects)	20 mg (or 15 mg for <55 kg subjects)	0†
2	45 mg	15 mg	0
3	30 mg	10 mg	0
4-6	25 mg	10 mg	0
7-8	20 mg	5 mg	0
9-10	15 mg	5 mg	0
11-14	10 mg	5 mg	0
15-20	5 mg	0	0
≥21	0	0	0

* Prednisone was supplied to study centers as 20 mg and 5 mg tablets, over-encapsulated with hard gelatin capsules.

†Placebo prednisone was given as matching gelatin capsules.

Supplemental Table 2. Treatment Response Based on BVAS for Subgroups*

	Placebo plus 60 mg prednisone control (N=23)	Avacopan plus 20 mg prednisone (N=22)	Avacopan without prednisone (N=22)
All Patients*	14 / 20 (70)	19 / 22 (86)	17 / 21 (81)
Disease Status			
Newly diagnosed patients	11 / 15 (73)	13 / 15 (87)	13 / 15 (87)
Relapsing disease	3 / 5 (60)	6 / 7 (86)	4 / 6 (67)
Type of AAV			
GPA	5 / 10 (50)	11 / 11 (100)	10 / 12 (83)
MPA	7 / 8 (88)	7 / 9 (78)	6 / 8 (75)
ANCA Status			
Anti-PR3 positive	6 / 10 (60)	10 / 10 (100)	6 / 8 (75)
Anti-MPO positive	7 / 10 (70)	9 / 12 (75)	11 / 13 (85)
Disease Location			
Renal ± other disease	13 / 19 (68)	18 / 21 (86)	16 / 20 (80)
Only non-renal disease	1 / 1 (100)	1 / 1 (100)	1 / 1 (100)
Background Treatment			
Cyclophosphamide	11 / 17 (65)	14 / 17 (82)	14 / 16 (88)
Rituximab	3 / 3 (100)	5 / 5 (100)	3 / 5 (60)

*Results are shown for n / N (%), where n = the number of treatment responders and N = the number of patients in the subgroup of patients specified. Treatment response is defined as a decrease from baseline to week 12 in BVAS of at least 50 percent and no worsening in any body system. AAV = ANCA-associated vasculitis; GPA = granulomatosis with polyangiitis; MPA = microscopic polyangiitis; PR3 = proteinase 3; MPO = myeloperoxidase.

Supplemental Table 3. Summary Results of the Short Form-36 version 2 Domains by Study Visit*

Domain	Study Visit	High Dose Steroids SOC Control (N=10)	Avacopan + Low-Dose Steroids (N=14)	Avacopan + No Steroids (N=9)
Role Physical	Base line	46±10	34±7	60±14
	Week 4	51±7	48±8	76±12
	Week 12	59±5	71±6	84±9
Bodily Pain	Base line	68±10	61±8	72±12
	Week 4	67±9	75±7	83±9†
	Week 12	81±6	81±6	93±7
General Health	Base line	45±7	55±4	66±5
	Week 4	48±5	60±5	52±6
	Week 12	51±4	59±5	62±8
Vitality	Base line	41±6	40±5	55±11
	Week 4	47±5	53±7	60±10
	Week 12	46±4	62±5†	71±8‡
Social Functioning	Base line	74±6	46±6	82±12
	Week 4	68±10	70±6	84±12
	Week 12	80±7	81±5	96±4
Mental Health	Base line	66±5	62±5	82±7
	Week 4	68±5	73±6	79±6
	Week 12	65±5	79±6‡	89±4‡
Reported Health Transition (decrease shows improvement)§	Base line	3.8±0.3	3.9±0.4	3.4±0.3
	Week 4	4.0±0.2	3.2±0.4	3.5±0.4
	Week 12	3.8±0.3	2.9±0.2†	2.9±0.4

*Results are shown for n, the number of patients with a measurement at the time point, and mean±SEM. The physical functioning and role emotional domain results are presented in Table 2.

† $P<0.05$, ‡ $P<0.01$ for change or percent change from baseline differences between avacopan and control groups.

§A decrease in Reported Health Transition corresponds to an improvement in health compared to one year ago.