

Vasculitis Landmark Trial Protocol Notes & Clinical Pearls

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1. CYCLOPS (2009) – Induction

IV cyclophosphamide pulses: 15 mg/kg every 2–3 weeks + prednisolone

Comparator: oral cyclophosphamide 2 mg/kg/day

2. RAVE (2010) – Induction

Rituximab: 375 mg/m² weekly ×4 + steroid taper (off by ~5 months)

Comparator: oral cyclophosphamide → azathioprine

3. RITUXVAS (2010) – Induction (renal AAV)

Rituximab: 375 mg/m² weekly ×4

2 IV cyclophosphamide pulses (at weeks 0 & 2)

4. MEPEX (2007) – Induction adjunct (severe renal)

Plasma exchange: 7 sessions / 14 days

Background: oral cyclophosphamide + steroids

5. PEXIVAS (2020) – Induction adjunct

Plasma exchange: 7 sessions / 14 days (vs none)

Steroids: standard vs reduced-dose taper

6. MAINRITSAN (2014) – Maintenance

Rituximab: 500 mg (day 0, 14, then months 6, 12, 18)

Comparator: azathioprine

7. RITAZAREM (2023) – Maintenance (relapsing AAV)

Rituximab: 1000 mg every 4 months ×5

Comparator: azathioprine

8. ADVOCATE (2021) – Induction (steroid-sparing)

Avacopan: 30 mg BID for 52 weeks

Comparator: prednisone taper (≈20 weeks)

CYCLOPS-2009

Pulse versus daily oral cyclophosphamide for induction

<https://pubmed.ncbi.nlm.nih.gov/19451574/>

Pulse cyclophosphamide, 15 mg/kg every 2 to 3 weeks , or daily oral cyclophosphamide, 2 mg/kg per day , plus prednisolone.

Patients received 3 intravenous pulses of cyclophosphamide, 15 mg/kg, given 2 weeks apart, followed by pulses at 3-week intervals (15 mg/kg intravenously or 5 mg/kg orally on 3 consecutive days, at the physician's discretion) until remission, and then for another 3 months.

The maximum dose per pulse was 1.2 g.

We reduced the cyclophosphamide dose by 2.5 mg/kg per pulse for persons age 60 to 70 years, 5 mg/kg per pulse for persons older than 70 years, and 2.5 mg/kg per pulse for persons with a serum creatinine level of 300 to 500 $\mu\text{mol/L}$ (3.4 to 5.7 mg/dL).

We reduced the dose of the subsequent pulse by 20% for patients with a leukocyte nadir of 2 to $3 \times 10^9 /\text{L}$ and 40% for those with a nadir of 1 to $2 \times 10^9 /\text{L}$.

The daily oral cyclophosphamide group received cyclophosphamide, 2 mg/kg per day, until remission, followed by 1.5 mg/kg per day for another 3 months.

The maximum oral dose was 200 mg, and we reduced the dose by 25% for persons older than 60 years and 50% for those older than 70 years.

At minimum, blood counts were checked weekly for the first month, twice-weekly for the second month, and monthly thereafter.

We withheld cyclophosphamide for persons with a leukocyte count less than $4 \times 10^9 /\text{L}$, then resumed therapy at a dose reduced by 25 mg/d when their count increased to greater than $4 \times 10^9 /\text{L}$.

Both groups continued the cyclophosphamide regimens for 3 months after remission, after which all patients received **azathioprine**, 2 mg/kg per day orally, until month 18 for remission maintenance. The maximum daily oral dose of azathioprine was 200 mg.

Both groups also received **prednisolone**, 1 mg/kg orally, tapered to 12.5 mg at the end of month 3 and to 5 mg at the end of the study (month 18).

Same remission rates

Less cumulative dose & toxicity with IV

BUT: higher relapse long-term with IV

RAVE-2010

Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis

<https://www.nejm.org/doi/full/10.1056/NEJMoa0909905>

rituximab (375 mg/m² per week for 4 weeks) as compared with cyclophosphamide (2 mg/kg/day) for remission induction. Glucocorticoids were tapered off; the primary end point was remission of disease without the use of prednisone at 6 months.

Patients in the control group who had a remission between 3 and 6 months were eligible to switch from cyclophosphamide to azathioprine (2 mg/kg/d).

Glucocorticoid regimen: one to three pulses of methylprednisolone (1000 mg each), followed by prednisone at a dose of 1 mg/kg/d. The dose was tapered so that by 5 months, all patients who had a remission without disease flares had discontinued glucocorticoids.

limitations.

enrolled only patients with severe ANCA-associated vasculitis who were ANCA-positive. Patients with alveolar haemorrhage severe enough to require ventilatory support and those with advanced renal dysfunction (serum creatinine level, >4.0 mg/dl [354 μmol/l]) were excluded.

Rituximab non-inferior to CYC for remission

Superior in relapsing disease (67% vs 42%)

👉 Practice-changing:

Rituximab became first-line, especially relapse / PR3

RITUXVAS-2010

Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis

<https://www.nejm.org/doi/full/10.1056/NEJMoa0909169>

Patients in the rituximab group received rituximab at a dose of 375 mg/m²/week, for 4 consecutive weeks, and intravenous cyclophosphamide at a dose of 15 mg/kg with the first and third rituximab infusions.

For patients in the rituximab group who had progressive disease within the first 6 months, a third dose of intravenous cyclophosphamide (at a dose of 15 mg/kg) was permitted.

Patients in the control group received a validated regimen of intravenous cyclophosphamide for 3 to 6 months, followed by azathioprine.

MAINRITSAN-2014

Rituximab versus Azathioprine for Maintenance in ANCA-Associated Vasculitis

<https://www.nejm.org/doi/full/10.1056/NEJMoa1404231>

Patients in complete remission after a cyclophosphamide–glucocorticoid regimen were randomly assigned to receive either 500 mg of rituximab on days 0 and 14 and at months 6, 12, and 18 after study entry or daily azathioprine until month 22.

Remission-induction : prednisone (starting at 1 mg/kg/d, followed by gradual tapering), preceded in some patients by methylprednisolone “pulses” (500 to 1000 mg daily for 1 to 3 consecutive days), and “pulse” cyclophosphamide (0.6 g/m² on days 0, 14, and 28, then 0.7 g/m² every 3 weeks for 3-6 additional pulses) until remission was attained.

After 4 to 6 months. At that time, and within a maximum of 1 month after the last cyclophosphamide pulse, eligible patients were enrolled and randomly assigned, in a 1:1 ratio, to receive maintenance therapy with rituximab or azathioprine.

rituximab (at a fixed 500-mg dose) on days 0 and 14 after randomization, and then at months 6, 12, and 18 after the first infusion. Patients in the control (azathioprine) group took azathioprine at a dosage of 2 mg/kg/d for 12 months, and then 1.5 mg/kg/d for 6 months and 1 mg/kg/d for 4 months.

Patients who had previously received rituximab or another form of biologic therapy were excluded.

PEXIVAS-2020

Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis

<https://www.nejm.org/doi/full/10.1056/NEJMoa1803537>

seven sessions of plasma exchange within 14 days or no plasma exchange.

Oral glucocorticoids commenced with prednisolone 1 mg/kg/day and were reduced over different lengths of time to 5 mg/day, such that cumulative oral glucocorticoid exposure in the first 6 months was 50% lower in patients allocated to the reduced-dose regimen than in those allocated to the standard-dose regimen.

All patients received the same glucocorticoid dosing from 6 to 12 months. Subsequent dosing was at the discretion of the treating physician.

Plasma exchange: received 60 ml/kg albumin replacement by means of centrifugation or filter separation; patients underwent seven treatments within 14 days after randomization. Plasma was allowed as replacement in patients at high risk for bleeding.

Largest AAV trial (n=704)

Two key findings:

PLEX → NO benefit on death/ESRD

Reduced steroid dose = non-inferior

👉 Massive paradigm shift:

PLEX mostly abandoned (except selected cases)

First strong RCT proving you can safely reduce steroids

weeks	Body weight		
	<50kg	50-75kg	>75kg
1	50	60	75
2	25	30	40
3-4	20	25	30
5-6	15	20	25
7-8	12.5	15	20
9-10	10	12.5	15
11-12	7.5	10	12.5
13-14	6	7.5	10
15-18	5	5	7.5
19-52	5	5	5
>52	Individual taper		

MEPEX 2007

Randomized Trial of Plasma Exchange or High-Dosage Methylprednisolone as Adjunctive Therapy for Severe Renal Vasculitis

https://journals.lww.com/jasn/abstract/2007/07000/randomized_trial_of_plasma_exchange_or_high_dosage.26.aspx

Both groups received oral cyclophosphamide 2.5 mg/kg per d (2 mg/kg per d for age > 60 yr), reduced to 1.5 mg/kg per d at 3 mo and stopped at 6 mo.

Azathioprine 2 mg/kg per d was commenced at 6 mo.

Oral prednisolone was tapered from 1 mg/kg per d at entry to 0.25 mg/kg per d by 10 wk, 15 mg/d at 3 mo and 10 mg/d from 5 to 12 mo.

A total of seven plasma exchanges within 14 d of study entry, a plasma exchange volume of 60 ml/kg on each occasion, and volume replacement with 5% albumin.

The use of fresh frozen plasma at the end of the procedure to replenish coagulation factors was recommended but not mandated for patients who were at risk for hemorrhage, for example after kidney biopsy.

PLEX improved short-term renal recovery

👉 Led to widespread PLEX use

ADVOCATE-2021

Avacopan for the Treatment of ANCA-Associated Vasculitis

<https://www.nejm.org/doi/full/10.1056/NEJMoa2023386>

Avacopan (30 mg twice daily) or matching placebo was given for 52 weeks, with 8 weeks of follow-up. Prednisone or a matched placebo was given on a tapering schedule for 20 weeks (60 mg per day tapered to discontinuation by week 21).

Glucocorticoid treatment during the screening period had to be tapered to 20 mg or less of prednisone equivalent before the patient began the trial, and this open-label glucocorticoid treatment was further tapered to discontinuation by the end of week 4 of the trial.

Patients were excluded if they had received more than 3 g of intravenous glucocorticoids within 4 weeks, or more than 10 mg per day of oral prednisone (or equivalent) for more than 6 weeks continuously.

avacopan was noninferior but not superior to prednisone taper with respect to remission at week 26 and was superior to prednisone taper with respect to sustained remission at week 52. 👉 First real **steroid-sparing alternative**.

RITAZAREM-2023

Rituximab versus azathioprine for maintenance of remission for patients with ANCA-associated vasculitis and relapsing disease: an international randomised controlled trial

[https://ard.eular.org/article/S0003-4967\(24\)00402-3/fulltext](https://ard.eular.org/article/S0003-4967(24)00402-3/fulltext)

Intravenous rituximab 1000 mg repeated every 4 months for five doses (months 4, 8, 12, 16 and 20 from enrolment).

Oral azathioprine 2 mg/kg/day for 24 months, then reduced by 50% and withdrawn at month 27.