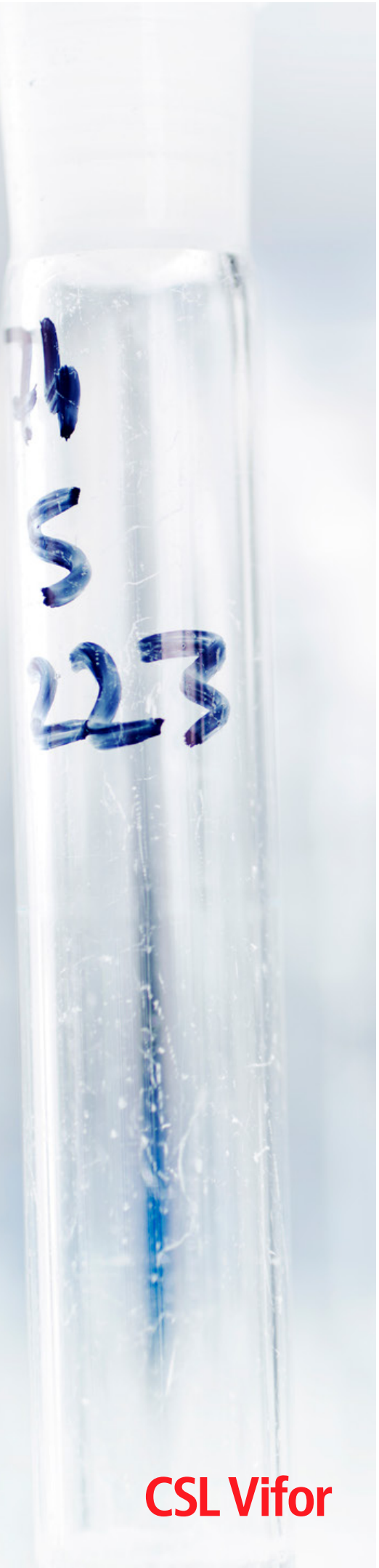
RAVE

RITUXIMAB IN ANCA-ASSOCIATED VASCULITIS



RTX WAS FOUND TO BE AS EFFECTIVE AS CYC FOR THE INDUCTION AND MAINTENANCE OF REMISSION, BUT REMISSION RATES REMAIN VARIABLE[1-3]

- Patient achievement and maintenance of full remission remains variable with current therapies
- 1 in 3 patients fail to achieve remission at 6 months without use of GCs, and 1 in 2 fail to sustain remission at 12 months
- Non-severe relapse is an under-recognised clinical problem; these patients suffer subsequent relapses resulting in high GC exposure

VIFOR FRESENIUS MEDICAL CARE RENAL PHARMA

CSL Vifor

INTRODUCTION

RAVE evaluated the achievement of full remission in patients using RTX or CYC.[1,2] Previous uncontrolled studies have suggested RTX is effective for remission induction and may be safer than the current standard therapy (CYC + GCs).[1]

For non-severe relapse data see page 3

STUDY AIM

Compare RTX and CYC for the induction of full remission (BVAS/WG=0 and have stopped glucocorticoids) by 6 months in AAV patients.[1]

STUDY EXTENSION

12-month treatment extension to evaluate the maintenance of remission through 18 months.[2]

STUDY DESIGN

Randomised, double-blind, double-dummy, multicentre, non-inferiority trial[1*]

6-month randomised treatment period[1]

Randomisation (N=197)

IV RTX 375 mg/m² once weekly for 4 weeks + daily placebo-CYC + GC† 1 mg/kg day (n=99)

Patients who had achieved remission between 3 and 6 months switched from placebo-CYC to placebo-AZA

Placebo-RTX once weekly for 4 weeks + CYC 2 mg/kg/day + GC† 1 mg/kg day (n=98)

Patients who had achieved remission between 3 and 6 months switched from CYC to AZA 2 mg/kg/day

Primary efficacy endpoint
BVAS/WG of 0 and successful completion of prednisone taper at 6 months
Secondary endpoints included
Rates of disease flares, BVAS/WG of 0 during treatment with <10 mg/day prednisone, cumulative GC doses, rates of AEs and SF-36 scores

12-month treatment extension period[2]

Patients who had completed the GC taper and had sustained disease remission received no further active treatment

Patients on assigned treatment: 6 months (n=82), 12 months (n=74), 18 months (n=61)

Patients who had completed the GC taper and were switched from CYC to AZA between 3 and 6 months remained on AZA 2 mg/kg/day until Month 18

Patients on assigned treatment: 6 months (n=78), 12 months (n=67), 18 months (n=63)

Primary efficacy endpoint
Achievement of complete remission by 6 months maintained through 18 months

RESULTS

At 6 months a greater percentage of the RTX treatment group were in full remission, the difference was non-inferior to the CYC group (P<0.001), with no significant difference in the AEs rates between groups.[1]

The percentage of patients maintaining remission through 18 months with RTX was slightly higher than CYC, RTX was non-inferior to CYC treatment (P<0.001), with no significant difference in AEs.[2]

PATIENTS ACHIEVING FULL REMISSION[1]

64% of RTX

53% of CYC

PATIENTS REMAINING IN FULL REMISSION[2]

48% of RTX

39% of CYC

PATIENTS REMAINING IN FULL REMISSION[3]

39% of RTX

33% of CYC

CONCLUSION

The RAVE study demonstrated that treatment with RTX + GCs was non-inferior to the standard treatment regimen for remission induction (CYC + GCs) at 6 months.[1] Despite the fact that patients in the RTX group who achieved remission at 6 months received no additional immunosuppression throughout the study, the RTX group was non-inferior to standard maintenance therapy (daily AZA) at 12 and 18 months for maintaining remission.[1,2]

In summary, RTX was found to be as effective as CYC and AZA for the induction of remission.[1,2]

REMISSION RATES REMAIN VARIABLE IN AAV; MANY PATIENTS DO NOT REACH OR REMAIN IN FULL REMISSION WITH CURRENT THERAPY[1,2]

INTRODUCTION

The second part of the RAVE study evaluated the outcomes of non-severe relapses in both treatment groups. In AAV patients most relapses experienced are non-severe, but relatively little data exists examining their importance and effect on clinical outcomes.[3]

For remission data see page 2

STUDY AIM

Analyse outcomes of patients who received GC treatment for non-severe relapses in the RAVE study.[3]

The sponsor of this study was:
Johns Hopkins University

STUDY DESIGN[3*‡]

Randomised, double-blind, double-dummy, multicentre, non-inferiority trial[1*]

Analysis of non-severe relapses

- Increase in BVAS/WG of ≤3 and the absence of major BVAS/WG items between months 1 and 18
- Three patients with BVAS/WG of 4 at relapse were included because their relapses were considered non-severe by their treating physicians
- 44 patients were analysed (RTX: n=23; CYC/AZA: n=21)

Treatment of non-severe relapses

- Prednisone increase (dose selected at investigator's discretion) without non-GC immunosuppressant change
- New dose maintained for 1 month before resumption of a specified taper every 2 weeks: 60 mg/day, 40 mg/day, 30 mg/day, 20 mg/day, 15 mg/day, 10 mg/day, 7.5 mg/day, 5 mg/day and 2.5 mg/day

RESULTS

Patients who experienced a non-severe relapse (n=44) were compared to patients who maintained full remission over 18 months (n=71). Non-severe relapse patients were more likely to be PR3-ANCA positive vs MPO ($p<0.02$), have a GPA diagnosis vs MPA ($p<0.01$), and have a history of relapsing disease at baseline, these patients had a greater mean cumulative GC dose than those who maintained remission, 6.7 g vs 3.8 g ($p<0.001$).[3]

Non-severe relapse patient outcomes (n=44)[3]

- An increase GC dose led to full remission in 80% of patients:
  - 30% maintained full remission through end of study
  - 70% had a second relapse (non-severe relapse: 55%), the mean time to second relapse was 9.4 months

CONCLUSION

RAVE demonstrated that increasing the GC dose was effective in restoring temporary remission in the majority of non-severe relapsing patients, but subsequent relapses were common. These patients were unable to sustain remission for long periods, resulting in high GC exposure.[3]

NON-SEVERE RELAPSE IN AAV IS AN UNDER-RECOGNISED CLINICAL PROBLEM LEADING TO HIGH GC EXPOSURE[3]

References & footnotes

AAV, ANCA-associated vasculitis; AEs, adverse events; ANCA, anti-neutrophil cytoplasmic antibody; AZA, azathioprine; BVAS, Birmingham Vasculitis Activity Score; CYC, cyclophosphamide; GC, glucocorticoid; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR3, proteinase 3; RTX, rituximab; WG, Wegener's Granulomatosis

*Multicentre, randomised, double-blind, double-dummy, noninferiority trial of rituximab (375 mg/m^2/week for 4 weeks; n=99; mean age at symptom onset: 54.0 years; male: 46%; GPA: 75%; MPA: 24%; indeterminate: 1%) vs. cyclophosphamide (2 mg/kg/day; n=98; mean age at symptom onset: 51.5 years; male: 54%; GPA: 76%; MPA: 24%) for remission induction in patients with severe AAV (PR3-/MPO-ANCA positive). Patients were enrolled between 30 December 2004 and 30 June 2008;[1] †Patients intially received 1–3 pulses of methylprednisolone (1000 mg each) followed by prednisone 1 mg/kg/day. The dose was tapered so that by 5 months, all patients who had a remission without disease flares had discontinued GCs;[1] ‡Patients who experienced non-severe relapses between months 1 and 18 (n=44; GPA: 91%; male: 48%) were treated with a prednisone increase without non-GC immunosuppressant change, followed by a taper.[3]

1. Stone JH, et al. *N Engl J Med* 2010;363(3):221–32.
2. Specks U, et al. *N Engl J Med* 2013;369(5):417–27.
3. Miloslavsky EM, et al. *Arthritis Rheum* 2015;67(6):1629–36.