Rituximab in ANCA- Associated Vasculitis

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Antineutrophil cytoplasmic antibodies (ANCAs) associated vasculitides (AAV) are a heterogeneous group of systemic necrotizing small vessel vasculitides.

More than 90% of AAV patients have circulating ANCAs.

AAV includes:

Granulomatosis with PolyAngiitis (GPA)

Microscopic Polyangiitis (MPA)

Eosinophilic Granulomatosis with PolyAngiitis (EGPA)

- AAV, was a frequently fatal disease before the introduction of high-dose glucocorticoids (GCs) and cyclophosphamide (CYC).
- More recent concerns have been the cumulative toxicity of these agents and management of a chronic relapsing disease course.

- Rituximab, a chimeric monoclonal antibody directed against the B-lymphocyte protein CD20, has been the most successful biologic response modifier to be used in AAV. Following the first report of its use in AAV in 2001, experience with rituximab for treatment of AAV has rapidly expanded.

Objectives

- Induction Therapy
- Re-Induction in relapsing vasculitis
- Maintenance Therapy

- 1- Rituximab in literatures
- 2- Rituximab in guidelines

Remission Induction Therapy in ANCA- Associated Vasculitis

&

Re-induction in Relapsing Cases

Principles of treatment of severe, systemic GPA

CYCLOPHOSPHAMIDE

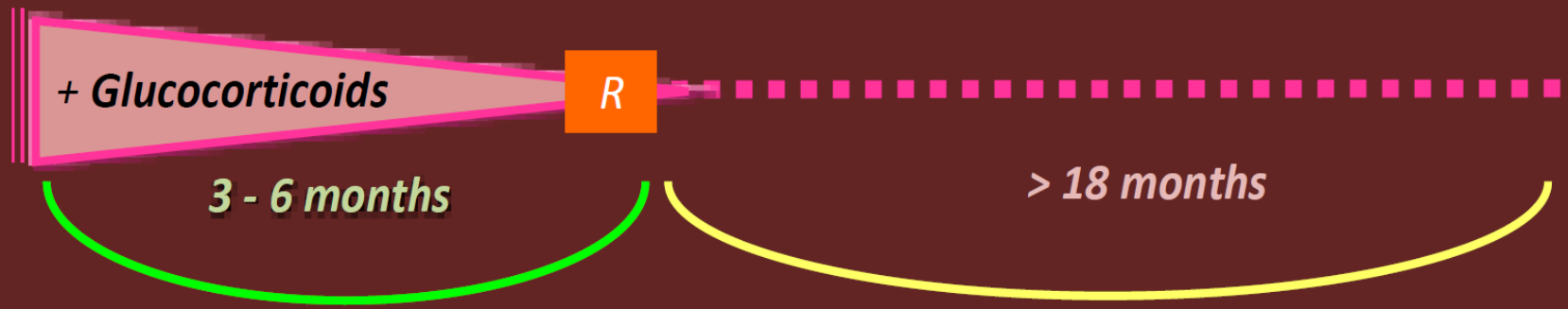
IV (pulse): 15 mg/kg on D1,15,29 then /3 wk

Oral (continuous): 2 mg/kg/d

- *AZATHIOPRINE* 2 mg/kg/d
- *METHOTREXATE* 0.3 mg/kg/wk
- *LEFLUNOMIDE* 20 mg/d
- *MYCOPHENOLATE MOFETIL* 2 g/d

RITUXIMAB

375 mg/m²/wk x 4 (or 1 g on D1 & 15)



± *Plasma exchange?*

INDUCTION ***MAINTENANCE***

Rituximab in ANCA-associated Vasculitis (RAVE) trial

RAVE trial, was the first multicenter, randomized, double-blind, controlled trial assessing the non-inferiority of RTX versus the standard of care (CYC) for remission induction in patients with severe AAV and GC weaning at 6 months.

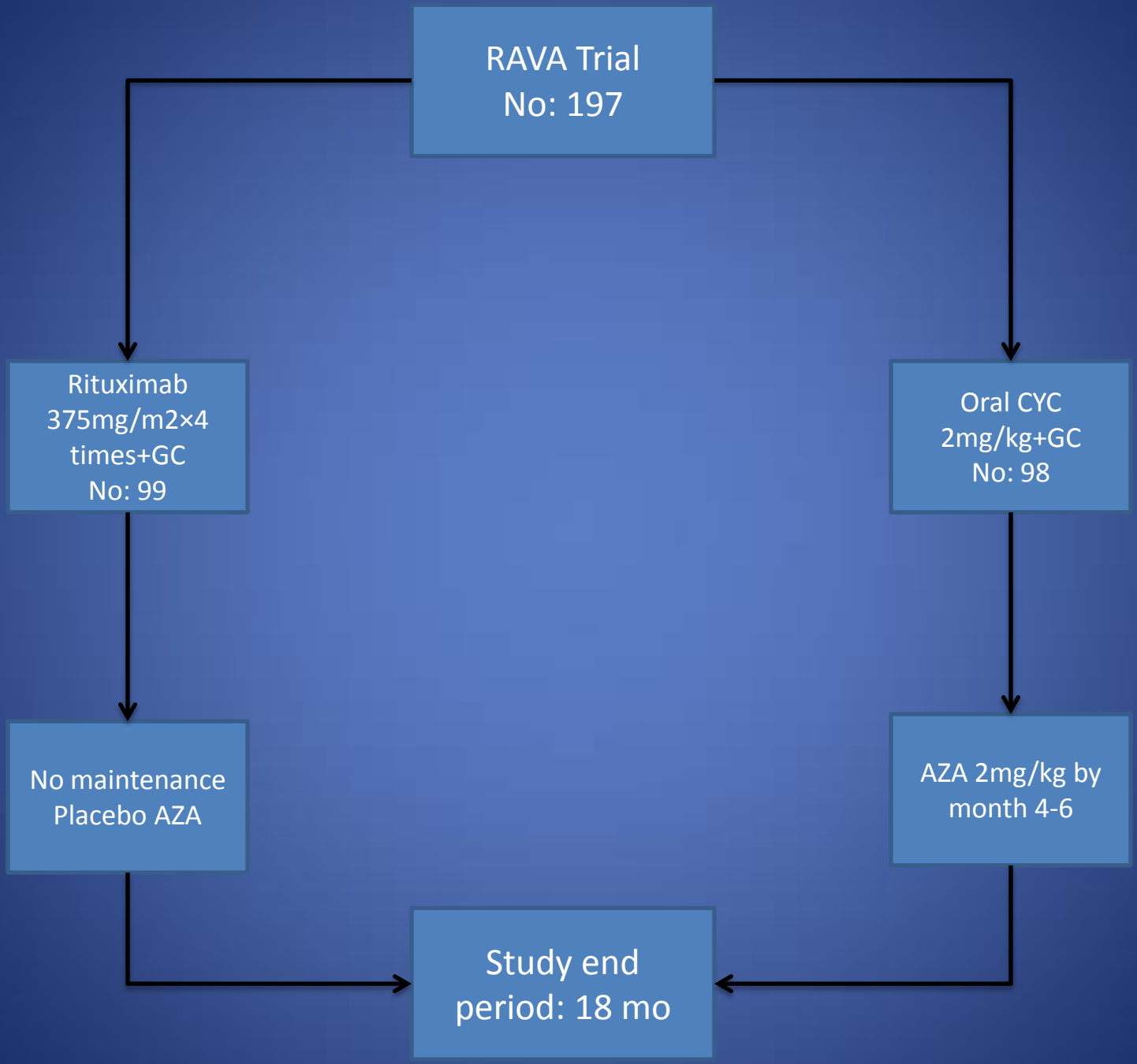
The patients met the following criteria:

severe GPA or MPA, newly diagnosed or relapsing disease, older than 15 years old, with active disease defined as a BVAS/WG equal to or above 3, ANCA-PR3+ or ANCA-MPO+.

The exclusion criteria were as follows:

Patients with limited disease, seronegative for ANCA, AH on mechanical respiratory assistance upon enrollment, and creatinine levels above 4 mg/dl.

N Engl J Med. 2010;363(3):221–32


RAVA Trial
No: 197
Rituximab
375mg/m2×4
times+GC
No: 99
Oral CYC
2mg/kg+GC
No: 98
No maintenance
Placebo AZA
AZA 2mg/kg by
month 4-6
Study end
period: 18 mo

RAVE Trial

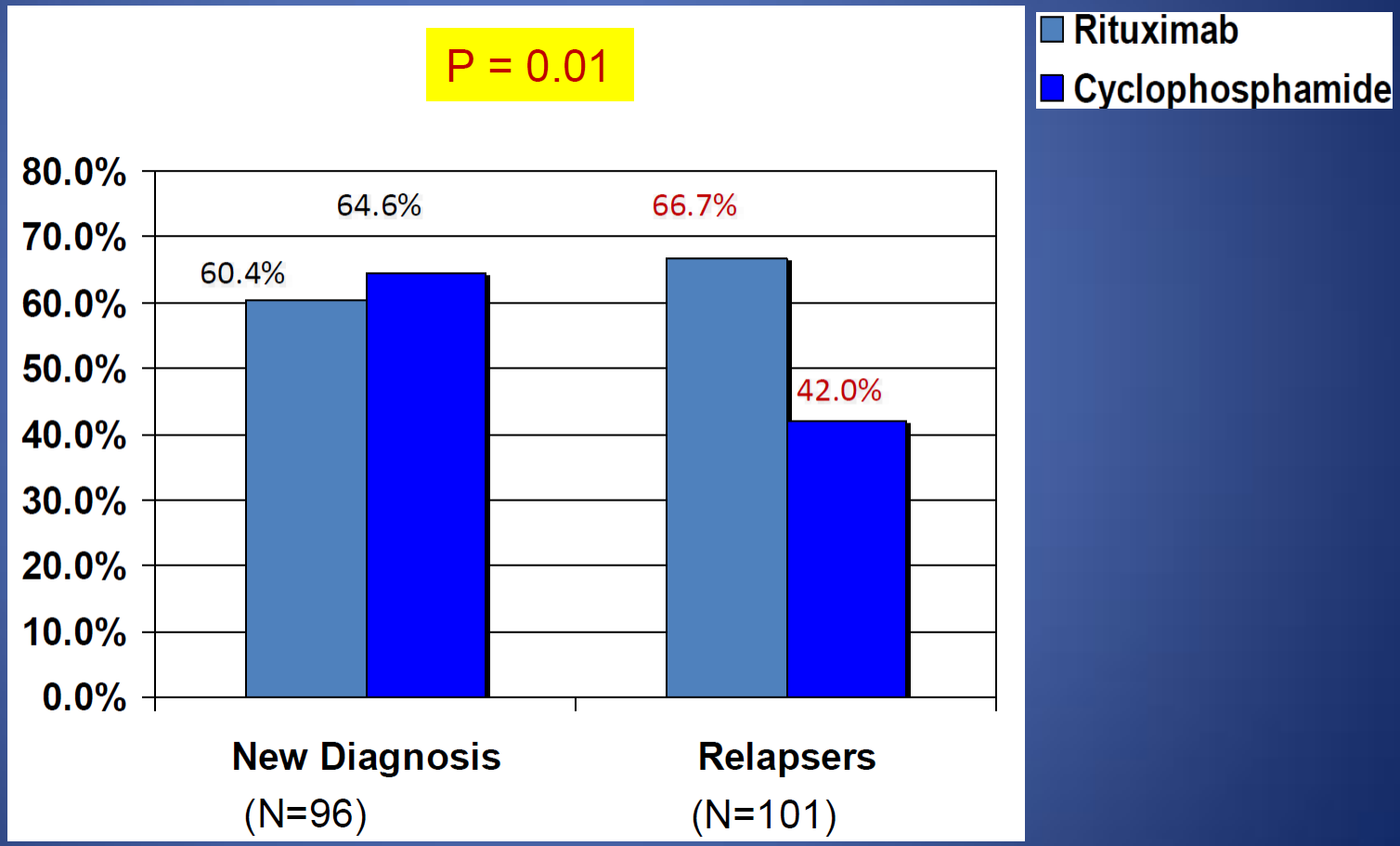
- Sixty-three out of 99 (64%) patients of the RTX group and 52 out of 98 (53%) patients of the control group met the primary end-point thus exhibiting the non-inferiority of RTX to induce remission in AAV.

RAVE Trial

- Although RAVE was not powered or designed to explore this specific question, when patients with relapsing disease were analyzed, RTX was superior to CYC for remission induction (67 vs. 42%, P≤ 0.01).

Better Responses in Relapsers

(VS newly diagnosed)

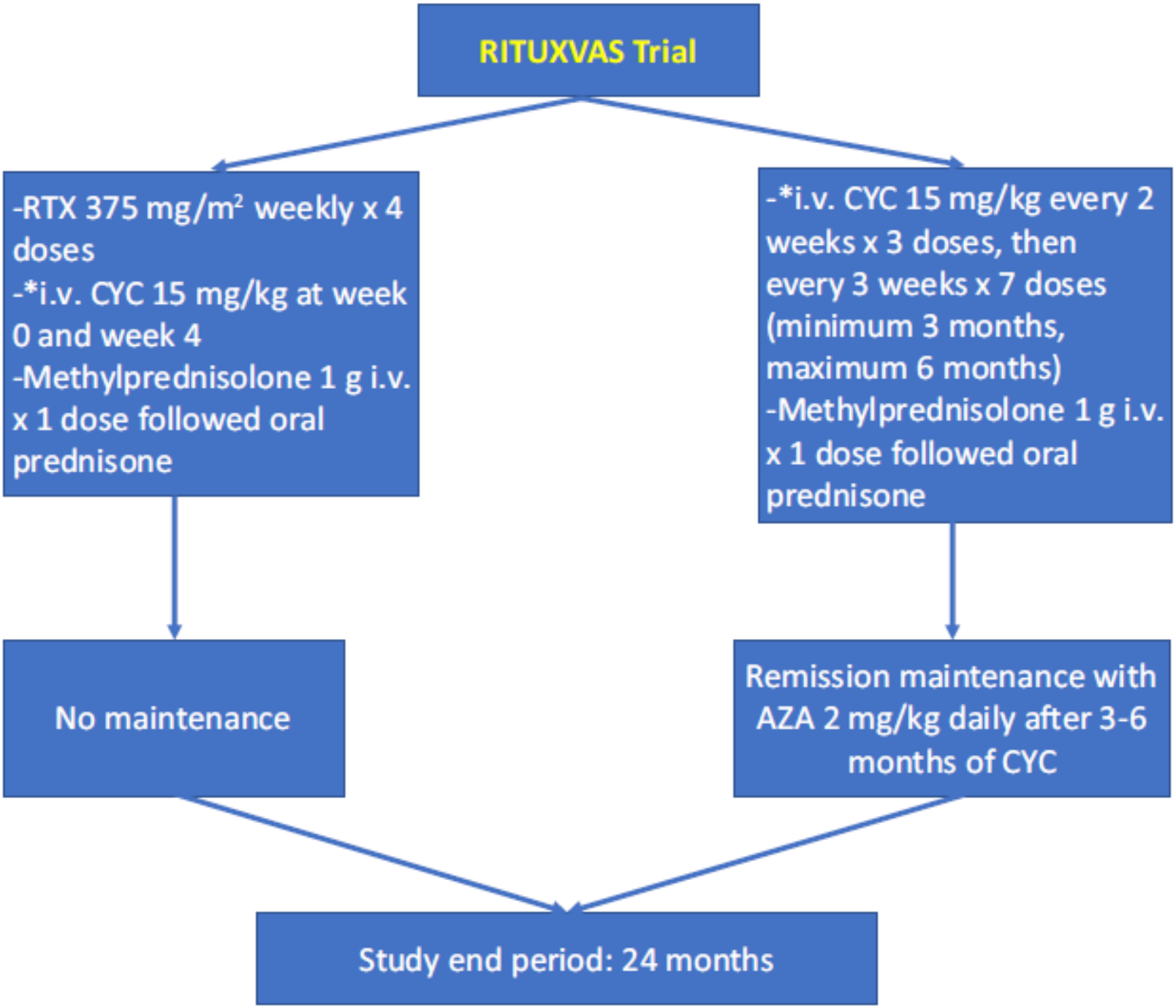


Stone et al, N Engl J Med 2010;363:221-32
Specks et al, N Engl J Med 2013;369:417-27

Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis (RITUXVAS) trial

- RITUXVAS trial was a multicenter, randomized, controlled, prospective, open trial published in 2010.
- Its primary objective was to assess whether the combined treatment with RTX and CYC in severe AAV associated with renal involvement was safer than and superior to the use of CYC alone.
- Forty-four newly diagnosed patients, ANCA+, and with renal involvement were included.

N Engl J Med 2010; 363:211-220


RITUXVAS Trial
-RTX 375 mg/m² weekly x 4 doses
-*i.v. CYC 15 mg/kg at week 0 and week 4
-Methylprednisolone 1 g i.v. x 1 dose followed oral prednisone
-*i.v. CYC 15 mg/kg every 2 weeks x 3 doses, then every 3 weeks x 7 doses (minimum 3 months, maximum 6 months)
-Methylprednisolone 1 g i.v. x 1 dose followed oral prednisone
No maintenance
Remission maintenance with AZA 2 mg/kg daily after 3-6 months of CYC
Study end period: 24 months

RITUXVAS trial

- The combined treatment of RTX+CYC was not superior to CYC alone.
- No differences were encountered in either mortality or infection rates.

N Engl J Med 2010; 363:211-220

Combination Therapy With Rituximab and Cyclophosphamide for Remission Induction

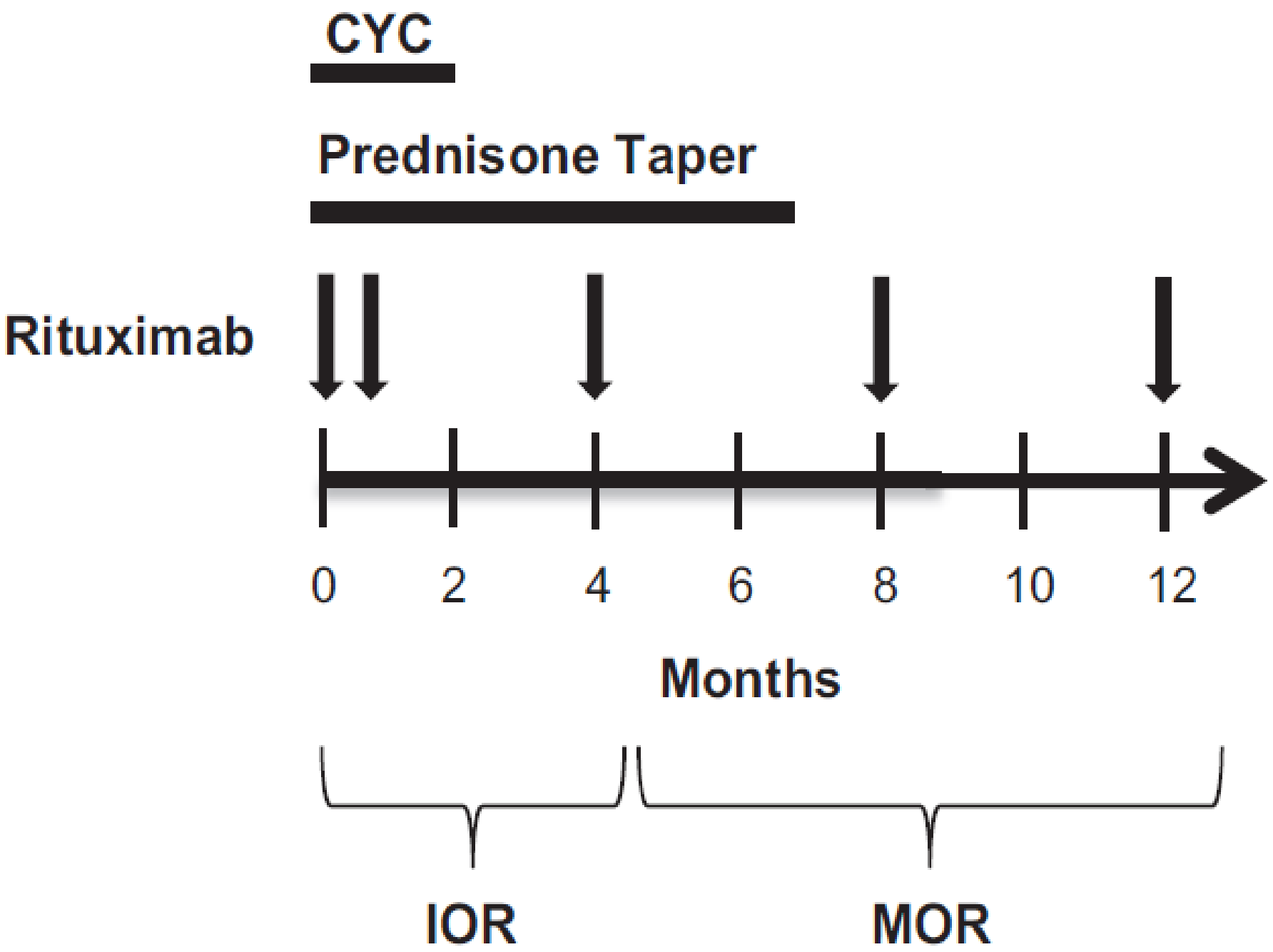
- The rationale for combining rituximab with cyclophosphamide is based on the differential effect of these medications across the B-cell lineage. Rituximab, an anti-CD20 monoclonal antibody, depletes precursors of autoantibody-producing cells, but has little direct effect on ANCA-producing plasmablasts and plasma cells that do not express CD20.
- The addition of cyclophosphamide to target autoantibody-producing plasmablasts and short-lived plasma cells allows for rapid tapering of high- dose steroids.
-

Kidney International Reports (2018) 3, 394–402

Combination Therapy With Rituximab and Cyclophosphamide for Remission Induction

- Patients were included in this retrospective study if they had newly diagnosed or relapsing ANCA vasculitis with a Birmingham Vasculitis Activity Score for Wegener Granulomatosis (BVAS-WG) ≥3 and received a standardized remission induction regimen.
- We identified 129 patients who met the inclusion criteria, 31% of whom also received plasma exchange (PLEX) for rapidly progressive glomerulonephritis (RPGN) or diffuse alveolar hemorrhage.
- The primary outcome was complete remission, defined as a BVAS-WG of 0 and a prednisone dose of ≤7.5 mg/d.

Kidney International Reports (2018) 3, 394–402


CYC
Prednisone Taper
Rituximab
0
2
4
6
8
10
12
Months
IOR
MOR

Combination Therapy With Rituximab and Cyclophosphamide for Remission Induction

- Cyclophosphamide was dosed at 2.5 mg/kg daily (maximum 175 mg/d) for 1 week, followed by 1.5 mg/kg daily (maximum 125 mg/d) for 7 weeks.

Kidney International Reports (2018) 3, 394–402

Combination Therapy With Rituximab and Cyclophosphamide for Remission Induction

- The daily prednisone dose was reduced to 15 mg by week 5 with the standardized regimen compared with week 11 in the RAVE trial protocol.
- Moreover, when used with rituximab, the dose and duration of cyclophosphamide was reduced.

Kidney International Reports (2018) 3, 394–402

Combination Therapy With Rituximab and Cyclophosphamide for Remission Induction

- In the RAVE trial, 71% of patients in the rituximab arm and 62% of patients in the control group reached the endpoint of remission at 6 months on less than 10 mg per day of prednisone per day.
- In patients treated with combination therapy, 118 patients (91%) were in remission using the same criteria despite inclusion of critically ill patients requiring PLEX.

Kidney International Reports (2018) 3, 394–402

Combination Therapy With Rituximab and Cyclophosphamide for Remission Induction

- The rate of serious infections in patients not receiving PLEX (0.017 per month) was similar to the number of serious infections in the RAVE trial (0.012 per month).

Kidney International Reports (2018) 3, 394–402

Limitations of the study

- the study is retrospective, is derived from a single center, and lacks a comparator group. In addition, 70% of patients had MPO-ANCA, making the results potentially less applicable to patients with PR3-ANCA.

Kidney International Reports (2018) 3, 394–402

Strengths of the study

- Strengths of the study include the relatively large size and inclusion of patients across the entire spectrum of disease encountered in clinical practice. In particular, the elderly and patients with severe organ-threatening disease requiring PLEX were included.

Kidney International Reports (2018) 3, 394–402

American Journal of Nephrology

Original Report: Patient-Oriented, Translational Research

Am J Nephrol 2015;41:296–301
DOI: 10.1159/000431336

Received: March 12, 2015
Accepted: May 6, 2015
Published online: June 2, 2015

Treatment of Severe Renal Disease in ANCA Positive and Negative Small Vessel Vasculitis with Rituximab

Shivani Shah[a] Zdenka Hruskova[c] Marten Segelmark[d] Matthew D. Morgan[e]
Jonathan Hogan[b] Steven K. Lee[a] Jessica Dale[f] Lorraine Harper[e]
Vladimir Tesar[c] David R.W. Jayne[g] Duvuru Geetha[a]

A multicenter, retrospective, cohort study was conducted between 2005 and 2014. Patients with new or relapsing disease with an estimated glomerular filtration rate (eGFR) of ≤20 ml/min/1.73 m(2) treated with rituximab and glucocorticoid induction with or without plasmapheresis were included. Fourteen patients met the inclusion criteria. The primary outcomes were rate of remission and dialysis independence at 6 months. The secondary outcomes were eGFR at 6 months, end-stage renal disease (ESRD), survival rates and adverse events.

American Journal of Nephrology

Original Report: Patient-Oriented, Translational Research

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Vladimir Tesar[c] David R.W. Jayne[g] Duvuru Geetha[a]

Patients with AAV and severe renal disease achieve high rates of remission and dialysis independence when treated with rituximab and glucocorticoids without cyclophosphamide.

ABSTRACT NUMBER: 18L

Rituximab As Re-Induction Therapy in Relapsing ANCA-Associated Vasculitis

Rona Smith[1], Rachel Jones[2], Ulrich Specks[3], Carol A McAlear[4], Kim Mynard[2], Simon Bond[2], David Jayne[5] and Peter A. Merkel[6], [1]Department of Medicine, University of Cambridge, Department of Medicine, University of Cambridge, Cambridge, United Kingdom, [2]Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom, [3]Mayo Clinic College of Medicine, Rochester, MN, [4]University of Pennsylvania, Philadelphia, PA, [5]Vasculitis and Lupus Clinic, Department of Medicine, University of Cambridge, Cambridge, United Kingdom, [6]Division of Rheumatology, University of Pennsylvania, Philadelphia, PA

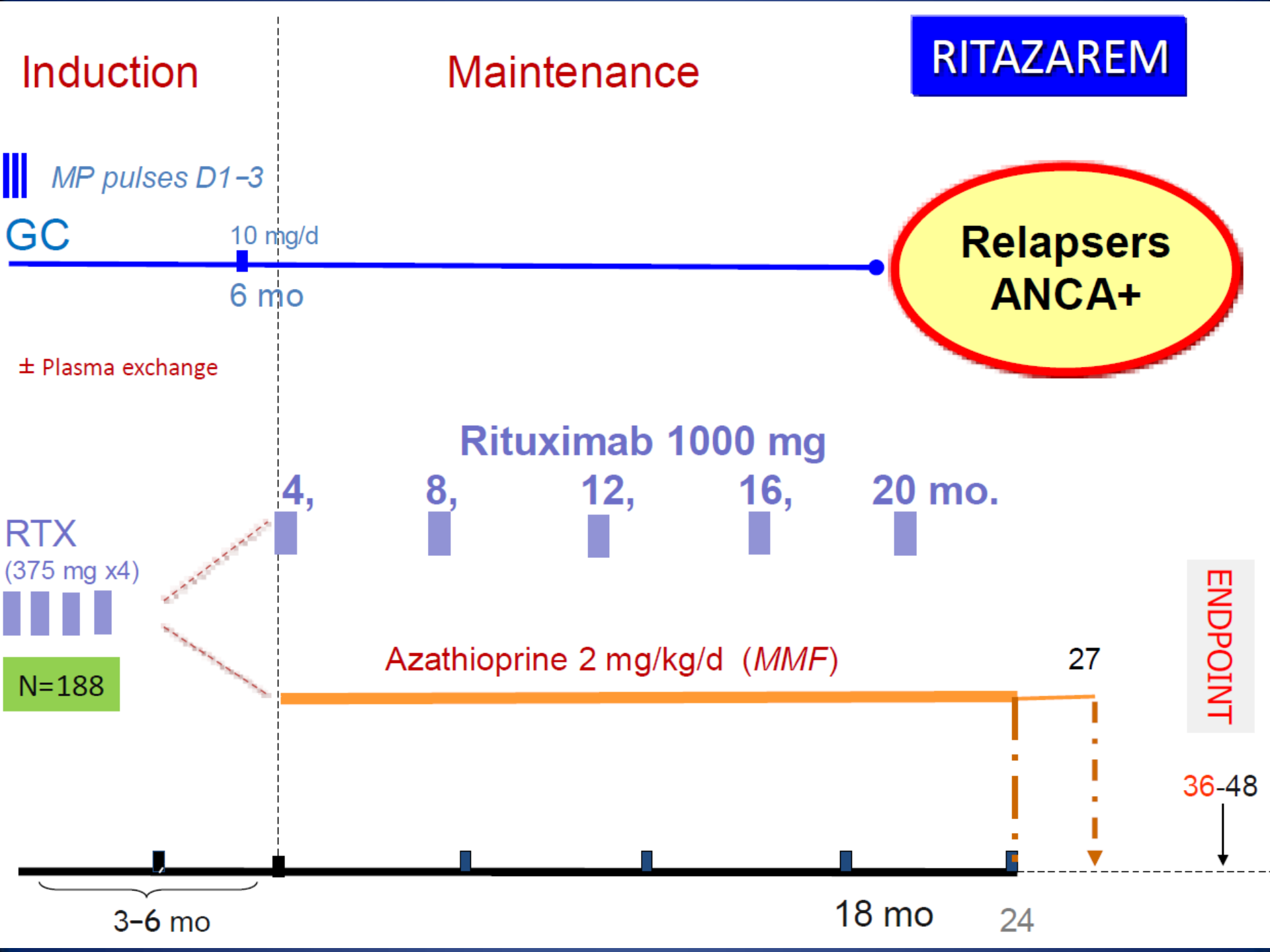
Meeting: 2017 ACR/ARHP Annual Meeting

Date of first publication: October 19, 2017

RITAZAREM is an international, randomized, controlled trial comparing rituximab with azathioprine for relapsing ANCA-associated vasculitis.

RITAZAREM

- 188 patients with granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) were enrolled and received remission-induction therapy with rituximab (4 x 375 mg/m^2) and glucocorticoid regimen.
- Patients who achieved remission (BVAS/WG ≤1 and prednisone ≤10 mg daily) by month 4 were randomized to either repeat dose rituximab (1 g every 4 months) or azathioprine (2 mg/kg/day) for a total treatment period of 24 months.

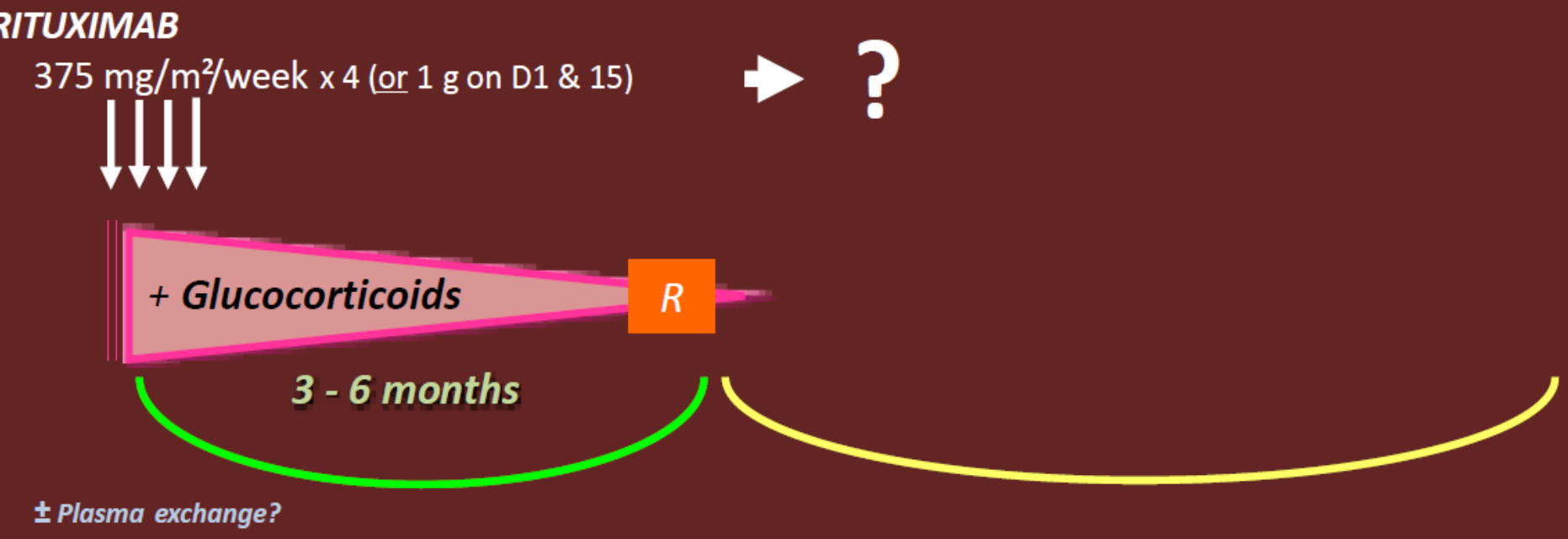

Induction
Maintenance
RITAZAREM
MP pulses D1–3
GC
10 mg/d
6 mo
Relapsers
ANCA+
± Plasma exchange
Rituximab 1000 mg
4, 8, 12, 16, 20 mo.
RTX
(375 mg x4)
N=188
Azathioprine 2 mg/kg/d (MMF)
27
ENDPOINT
36-48
3–6 mo
18 mo
24

RITAZAREM

- Data from the first phase of RITAZAREM, the largest reported cohort of patients with relapsing AAV, demonstrates that rituximab, in conjunction with glucocorticoids, is highly effective at re-inducing remission in patients with AAV who have relapsed, with an acceptable safety profile.
- The maintenance phase of the RITAZAREM trial is ongoing.

Maintenance Therapy in ANCA-Associated Vasculitis

Principles of treatment of severe, systemic GPA



RAVE Trial Extension

- Three years later, a RAVE 18-month extension was published with the aim of assessing long-term outcomes. No significant differences as to relapse, remission, or adverse event rates were encountered between the groups throughout the follow-up period.
- RTX proved to be superior to CYC at 6 and 12 months, but not at 18 months when B cell reconstitution took place.

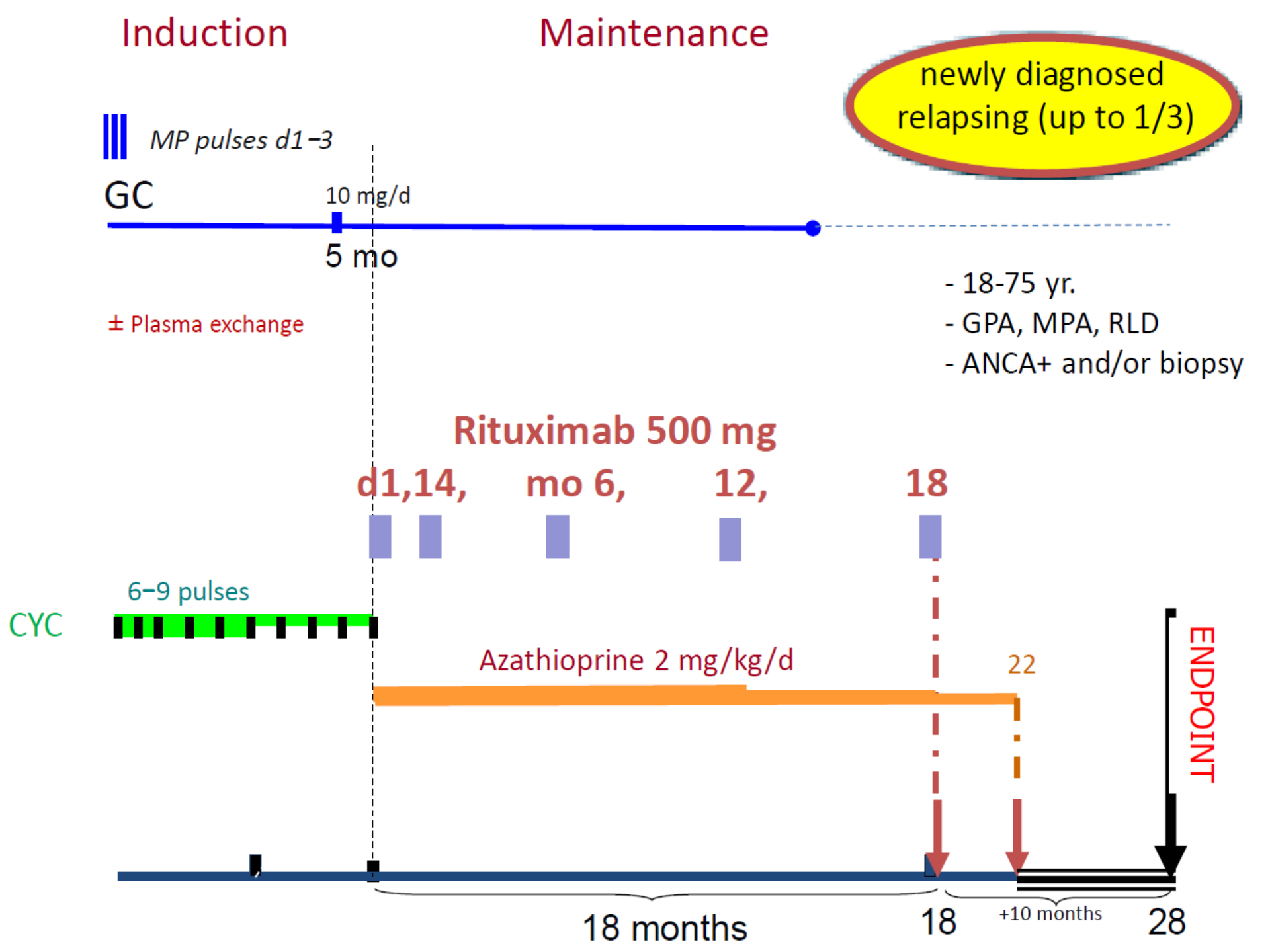
- The RAVE study extension then emphasized the need for maintenance of remission therapy after successful induction with RTX.

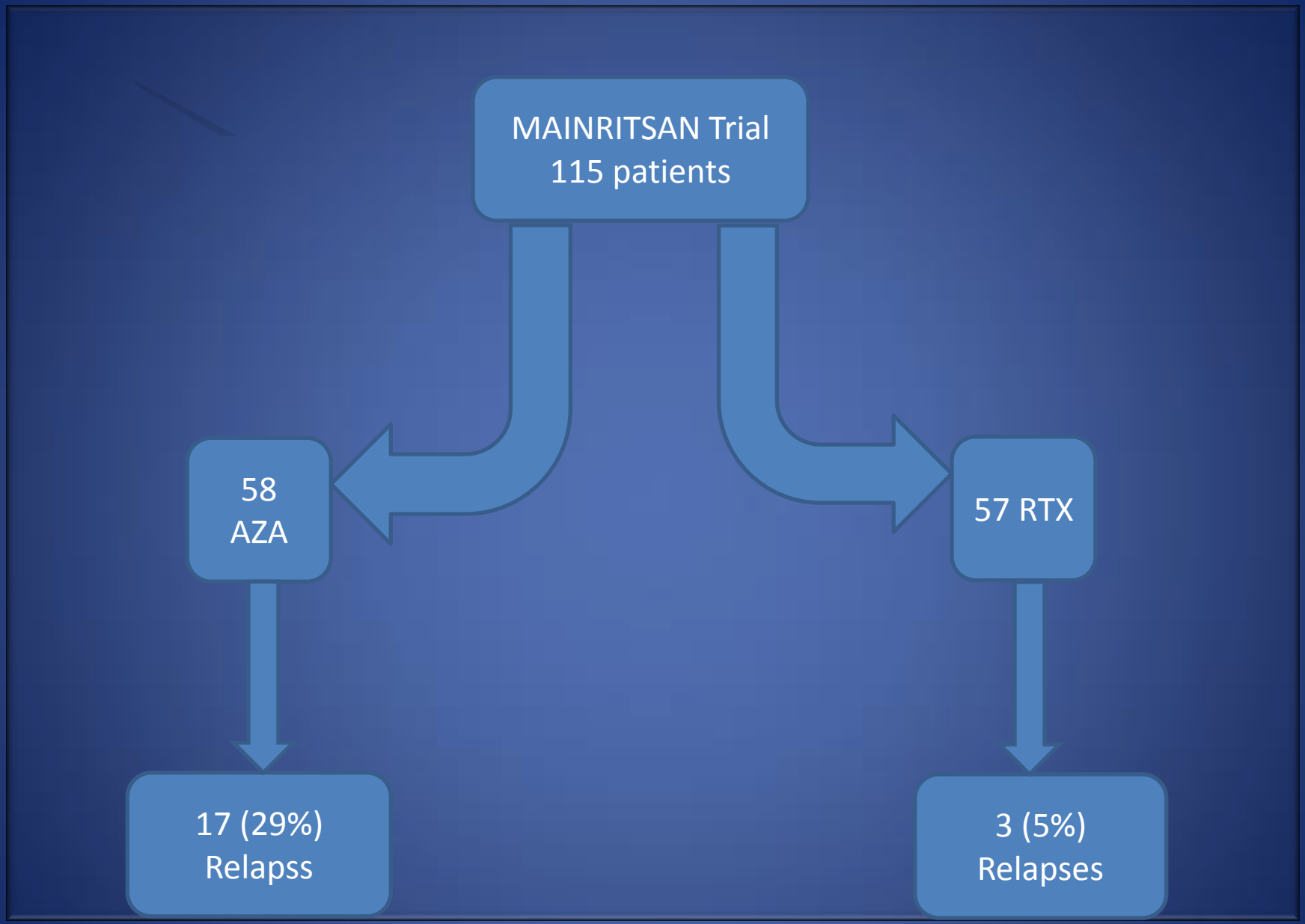
N Engl J Med. 2013;369(5):417–27

Rituximab versus azathioprine for maintenance in ANCA associated vasculitis (MAINRITSAN Trial)

- MAINRITSAN was the first randomized, controlled study with the purpose of evaluating whether a RTX-based maintenance regimen was more effective than and as safe as AZA for remission maintenance in AAV.

N Engl J Med. 2014;371(19):1771–80


Induction
Maintenance
newly diagnosed
relapsing (up to 1/3)
MP pulses d1–3
GC
10 mg/d
5 mo
± Plasma exchange
- 18-75 yr.
- GPA, MPA, RLD
- ANCA+ and/or biopsy
Rituximab 500 mg
d1,14, mo 6, 12, 18
6–9 pulses
CYC
Azathioprine 2 mg/kg/d
22
ENDPOINT
18 months
18
+10 months
28


MAINRITSAN Trial
115 patients
58
AZA
57 RTX
17 (29%)
Relapss
3 (5%)
Relapses

MAINRITSAN Trial

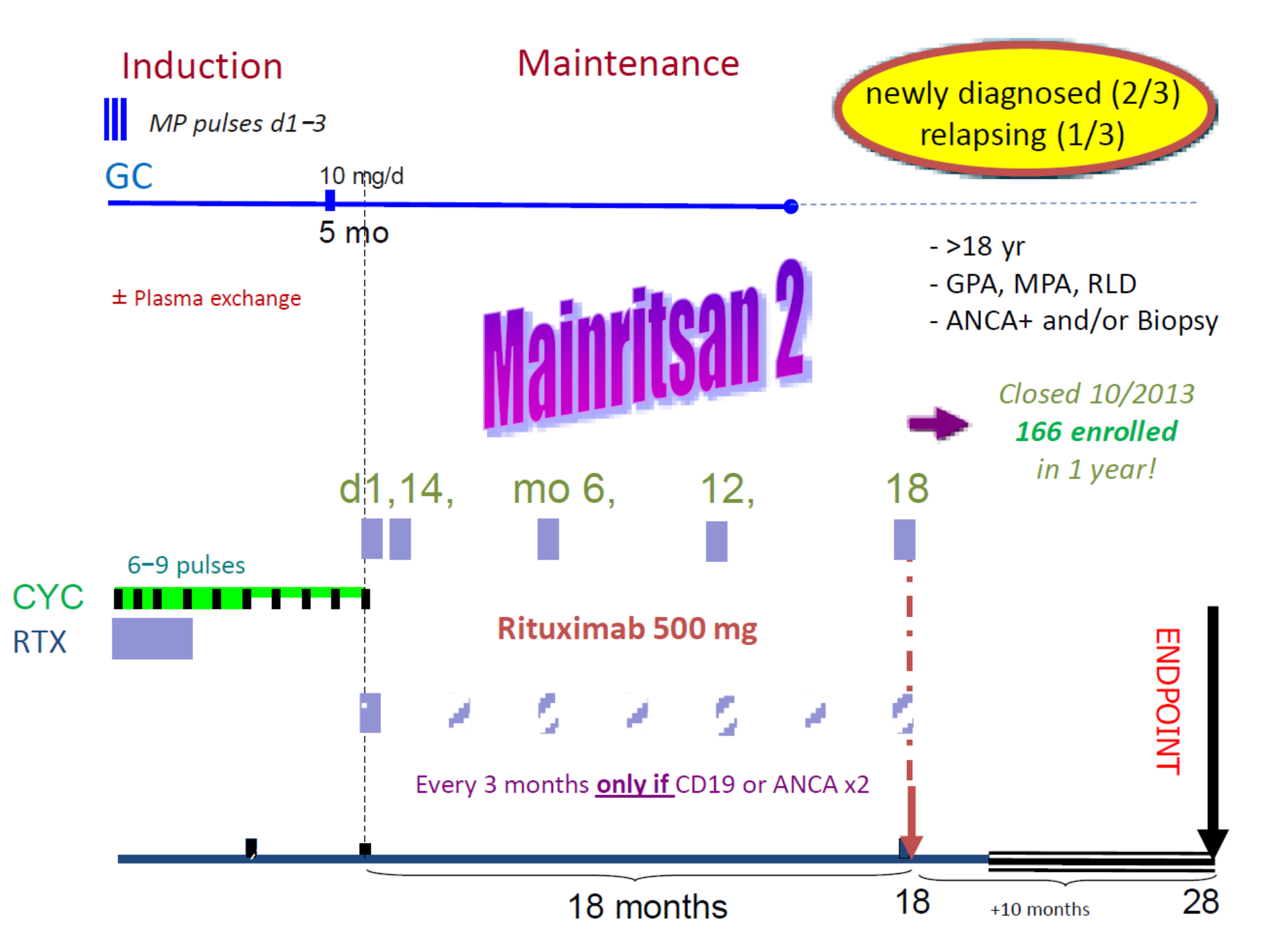
- RTX was superior to AZA for remission maintenance in AAV without increasing the adverse event rate.

N Engl J Med. 2014;371(19):1771–80

MAINRITSAN2 Trial

- Comparison of individually tailored versus fixed-schedule rituximab regimen to maintain ANCA-associated vasculitis remission: results of a multicentre, randomised controlled, phase III trial (MAINRITSAN2)

Ann Rheum Dis 2018; 77: 1144-1150


Induction
Maintenance
newly diagnosed (2/3)
relapsing (1/3)
MP pulses d1−3
GC
10 mg/d
5 mo
± Plasma exchange
- >18 yr
- GPA, MPA, RLD
- ANCA+ and/or Biopsy
Mainritsan 2
Closed 10/2013
166 enrolled
in 1 year!
d1,14,
mo 6,
12,
18
6−9 pulses
CYC
RTX
Rituximab 500 mg
Every 3 months only if CD19 or ANCA x2
ENDPOINT
18 months
18
+10 months
28

MAINRITSAN2 Trial

- AAV relapse rates did not differ significantly between individually tailored and fixed-schedule rituximab regimens. Individually tailored-arm patients received fewer rituximab infusions.

Ann Rheum Dis 2018; 77: 1144-1150

www.impactjournals.com/oncotarget/ Oncotarget, 2017, Vol. 8, (No. 32), pp: 52072-52077

Research Paper: Immunology

The "4 plus 2" rituximab protocol makes maintenance treatment unneeded in patients with refractory ANCA-associated vasculitis: A 10 years observation study

Dario Roccatello[1,2,*], Savino Sciascia[1,2,*], Daniela Rossi[1], Mirella Alpa[1], Carla Naretto[1], Massimo Radin[1], Roberta Fenoglio[2], Simone Baldovino[1,2] and Elisa Menegatti[1]

[1] Department of Clinical and Biological Sciences, Center of Research of Immunopathology and Rare Diseases, Coordinating Center of the Network for Rare Diseases of Piedmont and Aosta Valley, Department of Clinical and Biological Sciences, University of Turin, Turin, Italy

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[*] These authors have equally contributed to this manuscript

Correspondence to: *Dario Roccatello*, ***email***: *dario.roccatello@unito.it*

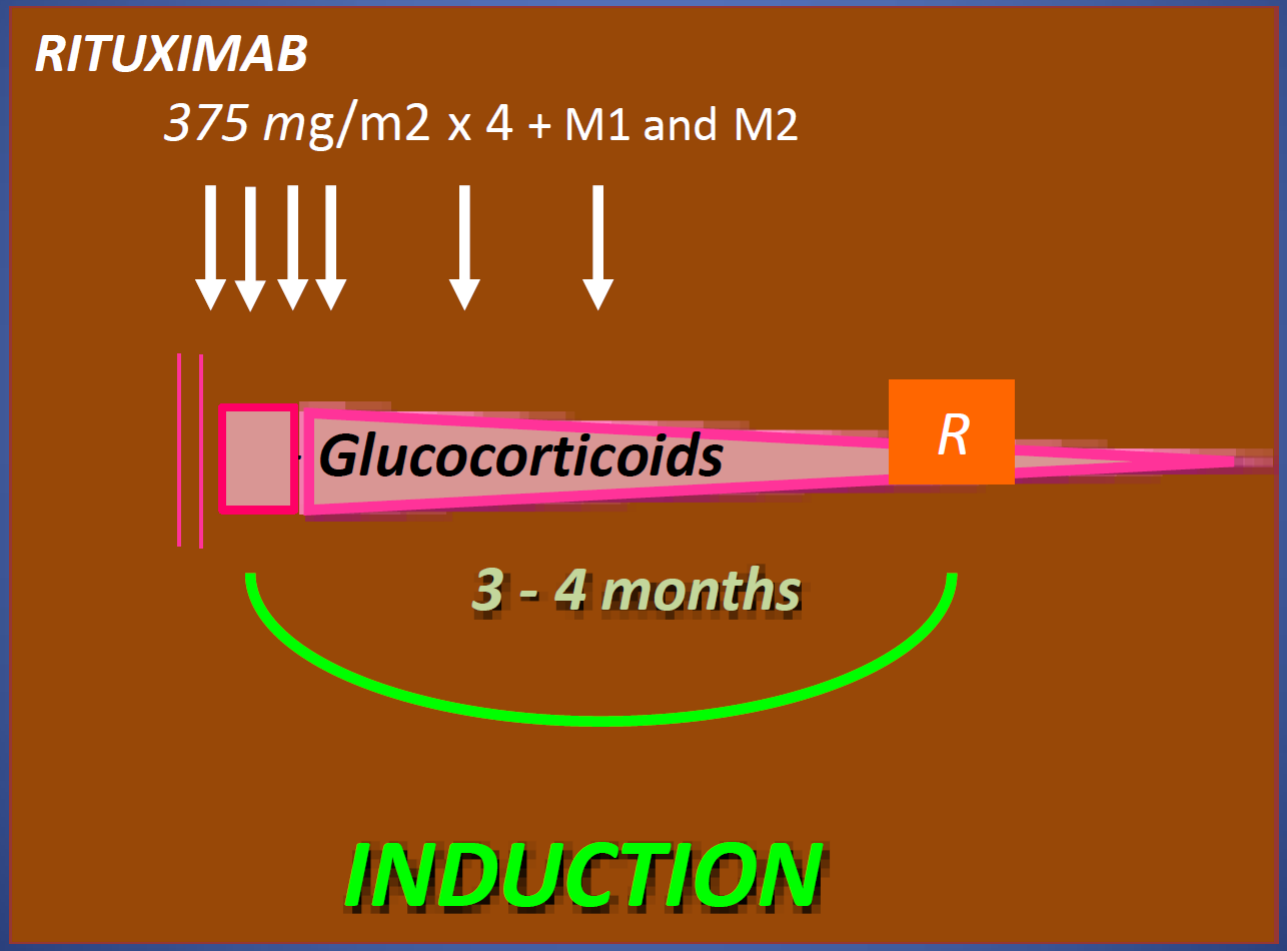
Keywords: rituximab, systemic vasculitis, ANCA-associated vasculitis, granulomatosis with polyangiitis, microscopic polyangiitis, Immunology and Microbiology Section, Immune response, Immunity

Received: *March 10, 2017* ***Accepted***: *April 19, 2017* ***Published***: *May 23, 2017*

The “4 plus 2” rituximab protocol

- Eleven patients with ANCA-associated vasculitis, mean age at the time of fist RTX cycle 67.5 years (range 45-81), were deemed eligible for RTX therapy.
- Follow up time (mean): 85 months

The “4 plus 2” rituximab protocol



The “4 plus 2” rituximab protocol

- Patients were not given any further immunosuppressive maintenance therapy after “4+2” RTX protocol, and oral prednisone was tapered to 5 mg/day by the end of the 3rd month after RTX.
- Seven out of 11 patients remained in remission for at least 60 months, and 4 did not experience any relapse at all.
- In the 7 relapsing patients a second cycle of infusion of RTX alone was given.
- Six months after treatment for relapse, 6 of 7 patients (86%) were in complete remission, while 1 (14%) patient with EGPA experienced a minor relapse, requiring small doses of mycophenolate mofetil (MMF).

The “4 plus 2” rituximab protocol

- Due to the delayed onset of relapse, our experience suggests that the policy of monitoring patients could be better than to administer fixed doses of RTX.

Rituximab in Guidelines

- British Society for Rheumatology (BSR) and British Health Professionals for Rheumatology (BHPR) (2014),
- the Canadian Vasculitis Research Network (CanVasc) (2015)
- The European League Against Rheumatism (EULAR)/European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) (2016)
- The Brazilian Society of Rheumatology (SBR)(2017)

Kidney International Reports (2018) 3, 1039–1049

KI REPORTS
KIReports.org
REVIEW

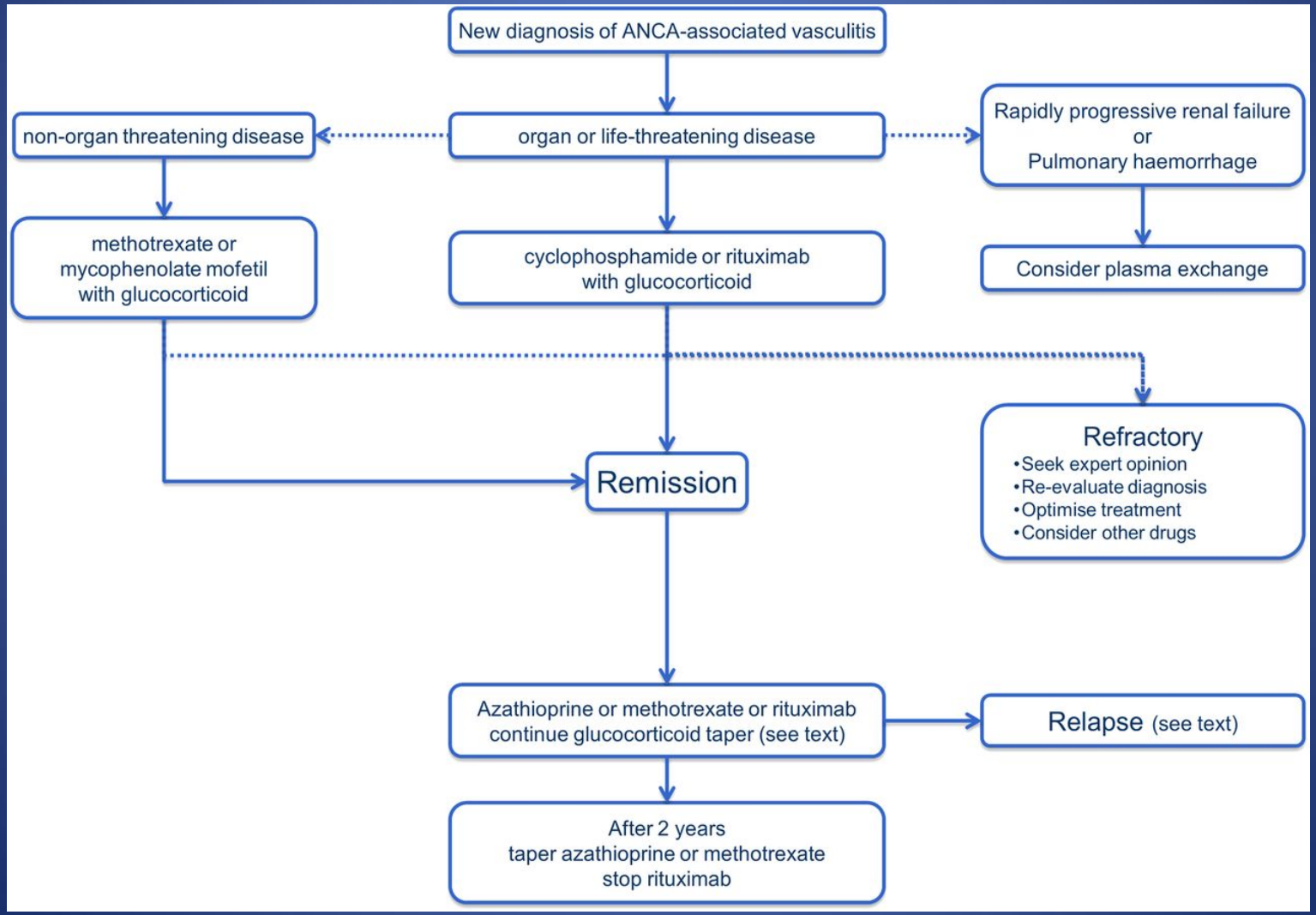
Comparisons of Guidelines and Recommendations on Managing Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

Duvuru Geetha[1], Qiuyu Jin[1], Jennifer Scott[2], Zdenka Hruskova[3], Mohamad Hanouneh[1], Mark A. Little[2], Vladimir Tesar[3], Philip Seo[1], David Jayne[4] and Christian Pagnoux[5]

[1]Department of Medicine, Johns Hopkins University, Baltimore, Maryland, USA; [2]Department of Medicine, Trinity Health Kidney Center, Tallaght Hospital, Dublin, Ireland; [3]Department of Medicine, Charles University Prague, Prague, Czech Republic; [4]Department of Medicine, University of Cambridge, Cambridge, UK; and [5]Department of Medicine, Mount Sinai Hospital, University Health Network, Toronto, Ontario, Canada

Kidney International Reports (2018) 3, 1039–1049 1039

Eular 2016 recommendation for management of ANCA- Associated Vasculitis



Comparisons of Guidelines

- None of the guidelines recommend against RTX as first-line induction treatment.
- The main drawbacks cited are access and/or cost barriers.
- EULAR notes that the data remain weakest among patients with EGPA.

Treatment of Refractory Disease

- Patients with severe AAV in whom remission induction with first-line CYC & GCs has failed should receive RTX (recommendation A by BSR/BHPR and recommendation C by EULAR and CanVasc).

Treatment of Disease Relapse

- The treatment of major and/or severe disease relapse is similar to initial induction treatment and generally consists of high-dose GCs & RTX or CYC (grade A recommendation by BSR/BHPR, EULAR/ERA-EDTA, and CanVasc), with RTX being the more recommended agent.

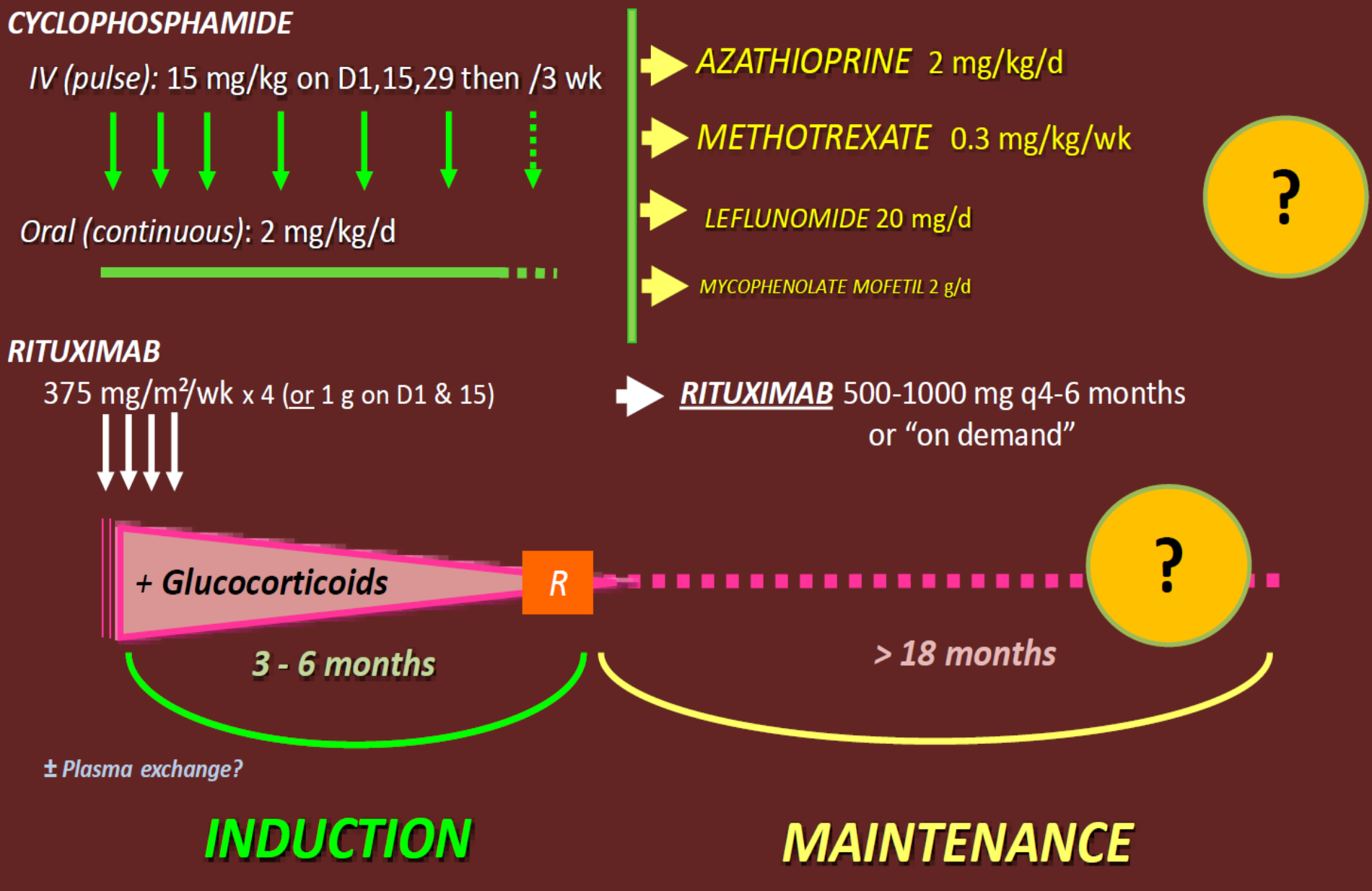
Monitoring of patients receiving Rituximab

- BSR/BHPR, EULAR/ERA-EDTA, and SBR discuss the importance of measuring serum Ig levels at baseline and before each course of RTX, with possible therapy modification or replacement therapy as needed.

Vaccination Recommendations

- BSR/BHPR and SBR specifically make vaccination recommendations, including hepatitis B, pneumococcal, and annual influenza vaccinations. BSR/BHPR recommends that the vaccine be administered at least 2 weeks before therapy but ideally at 4 to 6 weeks, whereas SBR recommends 3 weeks.

Principles of treatment of severe, systemic GPA



In conclusion

- RTX was not inferior to cyclophosphamide (CYC) for remission induction in AAV.
- It was superior to CYC in patients with relapsing or refractory disease.
- It was superior for remission maintenance in comparison with azathioprine (AZA).
- It seems that the policy of monitoring patients could be better than to administer fixed doses of RTX for maintenance therapy.
- Measurement of serum Ig levels at baseline and before each course of RTX is recommended.

- Additional studies for evaluation of combination therapy with rituximab and cyclophosphamide for induction therapy is recommended.


THANK YOU :)