

An Update on the Diagnosis and Management of Vasculitis

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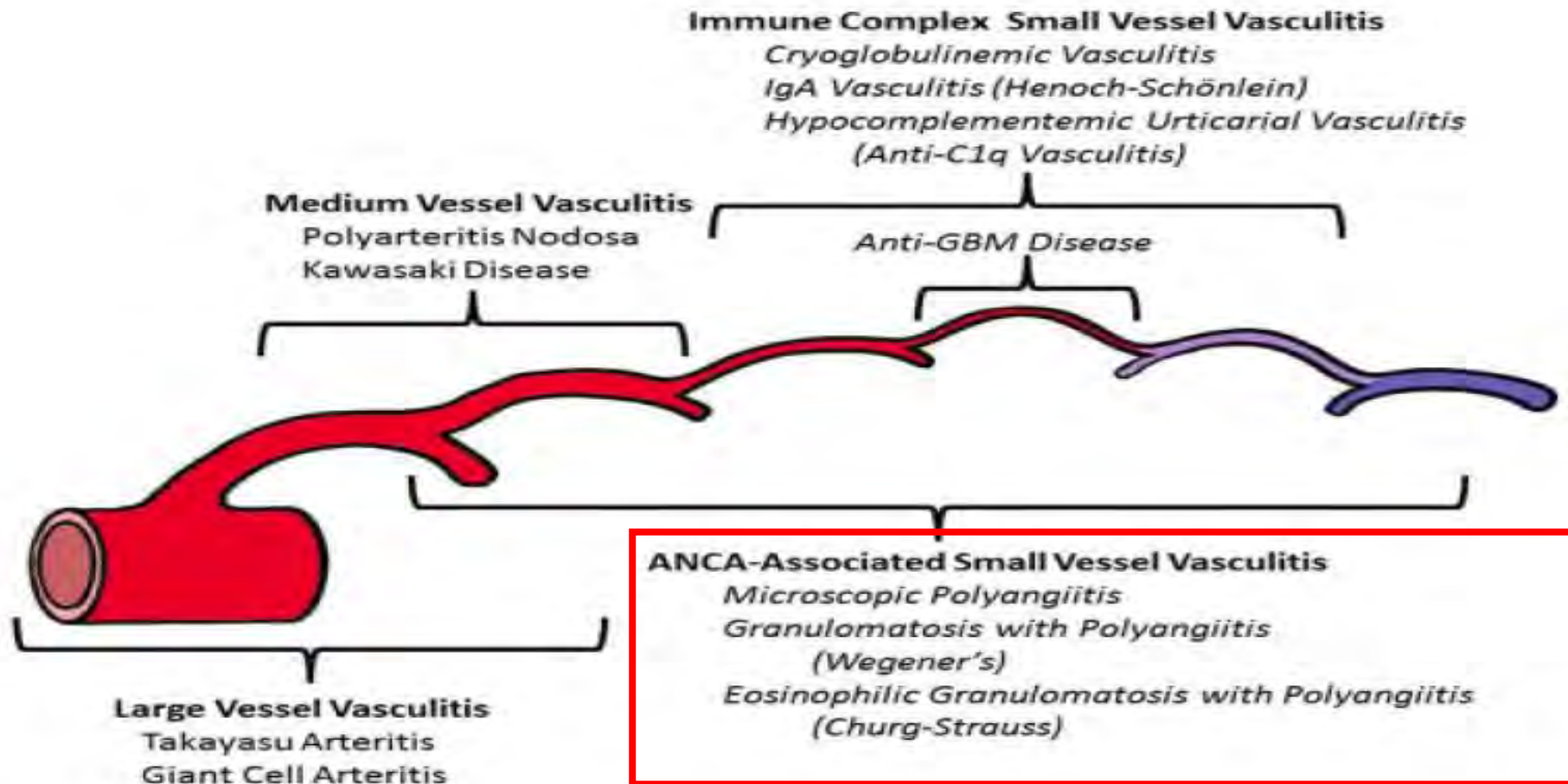
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Behçet's Disease Research Center

Istanbul, Turkey

Disclosures

- Abbvie - research grant, speaker
- Amgen - speaker
- Bayer – speaker, advisory board member
- Celgene – research grant, speaker, advisory board member
- Lilly – research grant
- Johnson & Johnson - advisory board member
- Novartis - speaker
- Silk Road Therapeutics - research grant
- UCB Pharma - research grant, speaker



- EULAR Recommendations for the management of AAV were updated
- New classification criteria were developed for AAV

14:15 - 15:30 EULAR Recommendations session

CHAIRS : ROBERT B.M. LANDEWÉ, DÉSIRÉE VAN DER HEIJDE

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EULAR recommendations for the management of ANCA-associated vasculitis: 2022 Update

Bernhard Hellmich
on behalf of the EULAR task force
Medius Kliniken – AKL Universität Tübingen
Kirchheim-Teck, Germany



Bernhard Hellmich

Update of the EULAR
Recommendations on the
management of ANCA-associated
vasculitis



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00:16

Systematic literature review informing the 2022 update of the EULAR recommendations for the management of ANCA-associated vasculitis: Focus on treatment strategies

Jan H. Schirmer¹, Beatriz Sanchez-Alamo², Sara Monti³, Bernhard Hellmich⁴, David R. W. Jayne⁵

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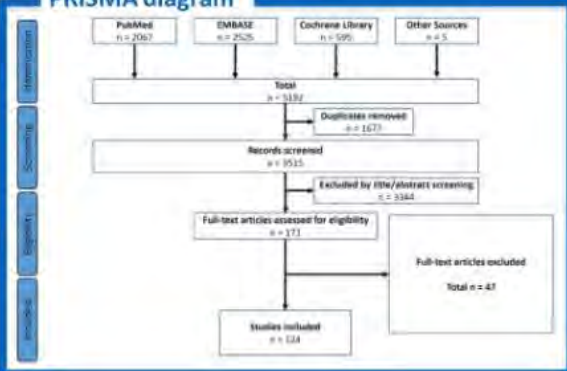
Background & Objectives

The 2016 European Alliance of Associations for Rheumatology (EULAR) recommendations for the management of ANCA-associated vasculitis¹ (AAV) have supported clinicians with comprehensive recommendations for the treatment of patients with granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA) in daily practice. During the past years, the publication of several high-impact randomized-controlled trials (RCT) further improved the standard of care (SOC) of AAV. The aim of this systematic review was to systematically identify and evaluate evidence to inform the 2022 update of the EULAR recommendations for the management of AAV.

Methods

- EULAR SOP²**
PICO questions, Oxford centre for evidence-based medicine 2009 level of evidence (LoE)
- Electronic databases**
PubMed, EMBASE, Cochrane Library, congress abstracts
- Update search**
Feb 2015 to Feb 2022
- 2 independent reviewers**

PRISMA diagram



Remission induction (GPA & MPA)

Rituximab & Cyclophosphamide

- One meta-analysis³ that included 2 RCTs comparing induction treatment with rituximab (RTX) or cyclophosphamide (CYC) reported similar rates for remission, serious adverse events (SAE) and death (LoE 1a).
- A post-hoc analysis⁴ of the RAVE⁵ trial (in which RTX treated patients were more likely to achieve remission in relapsing disease compared to CYC) showed that complete remission was initially achieved more frequently with RTX in proteinase 3 (PR3) – positive patients, especially those with relapsing disease and PR3-positivity (LoE 2b). Results from the non-controlled induction period of the RITAZAREM⁶ trial report high rates of remission after RTX induction in relapsing AAV (LoE 4).
- 2 meta-analyses^{3,7} of 4 RCTs suggested that induction with continuous oral compared to intravenous pulsed CYC results in lower relapse risk but higher rates of leukopenia (LoE 1a).
- One RCT⁸ found lower doses of CYC and glucocorticoids (GC) in vasculitis patients of 65 years or older to significantly reduce the rates of SAEs, whereas initial remission rates were equal and relapse risk was not significantly increased (LoE 1b).

Mycophenolate mofetil

- Results of 4 meta-analyses⁹⁻¹² showed similar rates of remission after induction treatment with mycophenolate mofetil (MMF) compared to CYC (LoE 1a). This includes 2 randomized-controlled trials^{13,14} (RCTs) published since the last guideline update that described no difference in initial remission but a higher relapse rate for MMF in one study.

Glucocorticoids & Avacopan

Glucocorticoids

- 2 RCTs^{15,16} demonstrated that reduced GC doses and tapering schemes were noninferior compared to standard / high dose GC during remission induction treatment for GPA and MPA (LoE 1b). For EGPA no trial comparing GC dosing schemes was available.

Avacopan

- In 3 RCTs¹⁷⁻¹⁹ avacopan instead of GC during induction treatment led to similar rates of remission in GPA and MPA and was superior at week 52 in a phase 3 trial¹⁸ (LoE 1b).

Remission maintenance (GPA & MPA)

Conventional immunosuppressives

- One meta-analysis³ of 2 RCTs^{20,21} that were published since the last update of the EULAR recommendations showed lower relapse rates for extended duration of azathioprine (AZA) treatment compared to standard duration (LoE 1a).
- Results from one RCT²² comparing remission maintenance treatment with methotrexate (MTX) and CYC showed no difference in relapse frequency (LoE 1b).

Biologic agents

- Preliminary results from one RCT²³ (published in abstract format) show reduction of relapse risk for RTX compared to AZA as maintenance agent used after induction with RTX (LoE 1b).
- One RCT²⁴ demonstrated prolonged relapse-free survival, if maintenance treatment with RTX was given for 36 instead of 18 months (LoE 1b).
- 2 RCTs described biomarker-driven maintenance treatment strategies with RTX. In one trial²⁵, relapse risk was not significantly increased when RTX was given upon reconstitution of B cells or increase of ANCA. Preliminary data from another trial (published as abstract)²⁶ suggest that B cell-driven retreatment with RTX prevents relapses more efficient compared to ANCA-driven retreatment (LoE 1b).
- Belimumab added to standard of care for maintenance treatment showed no additional reduction of relapse-risk in one RCT²⁷ (LoE 1b).

Trimethoprim / Sulfamethoxazole

- 2 meta-analyses^{3,28} including 2 RCTs (and non-randomized intervention studies in one meta-analysis) found no statistically significant reduction of relapse risk for trimethoprim-sulfamethoxazole (LoE 1a).

References

1. Yates et al. Ann. Rheum. Dis. 2016. 2. van der Heijde et al. Ann. Rheum. Dis. 2014. 3. Walters et al. Cochrane Database Syst. Rev. 2020. 4. Unizony et al. Ann. Rheum. Dis. 2015. 5. Specks et al. N. Engl. J. Med. 2013. 6. Smith et al. Ann. Rheum. Dis. 2020. 7. Springer JM et al. ACR Open Rheumatol. 2021. 8. Pagnoux et al. Arthritis Rheumatol. 2015. 9. Berti A et al. Nephrol. Dial. Transplant. 2021. 10. Kuzuya et al. RMD Open 2020. 11. Song & Lee YH. Z. Rheumatol. 2021. 12. Xiong et al. 2021. 13. Jones et al. Ann. Rheum. Dis. 2019. 14. Tulin J et al. Clin. J. Am. Soc. Nephrol. 2019. 15. Walsh et al. N. Engl. J. Med. 2020. 16. Furuta et al. JAMA 2021. 17. Jayne et al. J. Am. Soc. Nephrol. 2017. 18. Jayne et al. N. Engl. J. Med. 2021. 19. Merkel et al. ACR Open Rheumatol. 2020. 20. Sanders et al. Nephrol. Dial. Transplant. 2016. 21. Karras et al. Ann. Rheum. Dis. 2017. 22. Maritati et al. PLoS One 2017. 23. Smith et al. Ann. Rheum. Dis. 2020 Suppl 1. 24. Charles et al. Ann. Intern. Med. 2020. 25. Charles et al. Ann. Rheum. Dis. 2018. 26. Zonzi et al. J. Am. Soc. Nephrol. 2017. 27. Jayne et al. Arthritis Rheumatol. 2019. 28. Monti et al. Rheumatol. Oxf. 2021. 29. Walsh et al. BMJ 2022. 30. Puechal et al. Arthritis Rheumatol. 2017. 31. Terrier et al. Arthritis Rheumatol. 2021. 32. Wechsler et al. N. Engl. J. Med. 2017. 33. Ayarlar A. gidiu.

Plasma exchange (GPA & MPA)

Plasma exchange

- One large RCT¹⁵ found no significant reduction of the combined endpoint end-stage kidney-disease (ESKD) or death when plasma exchange (PLEX) was added to SOC. A subgroup analysis showed no significant benefit of PLEX in alveolar hemorrhage (LoE 1b).
- A meta-analysis²⁹ of 9 RCTs (including the above mentioned) reported reduced rates of ESKD at 1 year, but not at 3 years and a significant increase of serious infections for PLEX (LoE 1a).

Eosinophilic granulomatosis with polyangiitis

Azathioprine

- One RCT³⁰ including necrotizing vasculitides without predictors of poor prognosis (Five factor score / FFS = 0) found remission failure and relapse risk rates not significantly reduced, if GC and AZA were initially given, compared to GC monotherapy (LoE 1b).

Rituximab

- One RCT³¹ (published as abstract) compared RTX and GC with SOC for remission induction in EGPA. If FFS was ≥ 1 , patients received additionally CYC in the SOC group or CYC placebo in the RTX group. Remission rates were similar (LoE 1b).

Mepolizumab

- One RCT³² compared mepolizumab and SOC to placebo and SOC in relapsing and refractory EGPA. Mepolizumab increased the rates of remission and showed GC-sparing properties (LoE 1b).

Conclusion

Results of this systematic literature review provide a comprehensive update of the available evidence to guide the 2022 update of the EULAR recommendations for the management of AAV. The presented results are preliminary.

Overarching principles

- Patients with AAV should be offered best care which must be based on **shared decision making** between the patient and the physician considering efficacy, safety and costs.
- Patients should have access to **education** focusing on the impact of AAV and its prognosis, key warning symptoms and treatment (including treatment-related complications)
- Patients with AAV should be **periodically screened for treatment related adverse events and co-morbidities**.
- We recommend **prophylaxis and life-style advice** to reduce treatment related complications and other comorbidities
- AAV are rare, heterogeneous, and potentially life and organ threatening diseases, and thus require **multidisciplinary management** by centers with, or with ready **access to specific vasculitis expertise**

Diagnosis

- A positive biopsy is strongly suggestive of a diagnosis of vasculitis and we recommend biopsies to assist in establishing a new diagnosis of AAV and for further evaluation of patients suspected of having relapsing vasculitis.

Level of evidence: 3b

Grade of recommendation: C

Level of agreement: 8.7 ± 1.9

- In patients with signs and/or symptoms raising suspicion of a diagnosis of AAV, we recommend testing for both PR3 and MPO ANCA using a high quality antigen-specific assay for the primary method of testing.

Level of evidence: 1a

Grade of recommendation: A

Level of agreement: 10.0 ± 0

Treatment – GPA/MPA (organ- or life-threatening)

- For induction of remission in patients with new onset or relapsing GPA/MPA with organ- or life-threatening disease, we recommend treatment with a combination of glucocorticoids and either rituximab or cyclophosphamide.

Level of evidence: 1a
Grade of recommendation: A
Level of agreement: 9.6 ± 0.8

- Rituximab is preferred in relapsing disease

Level of evidence: 2b
Grade of recommendation: B
Level of agreement: 9.6 ± 0.8

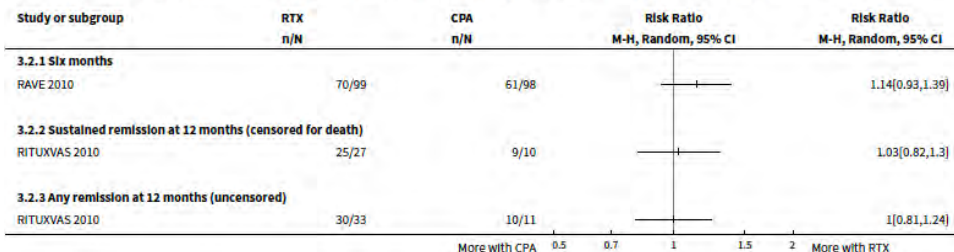
[Intervention Review]

Interventions for renal vasculitis in adults

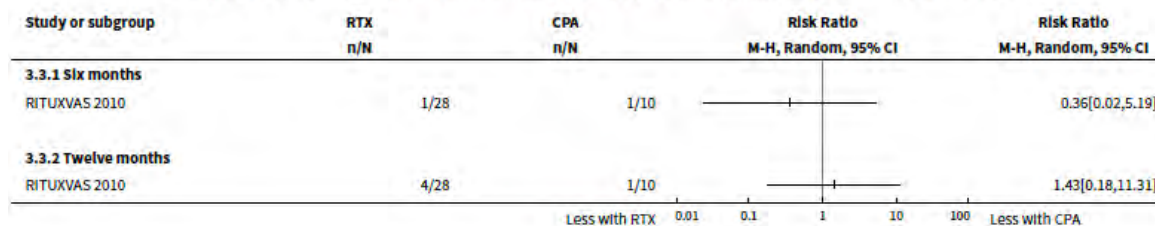
Giles D Walters¹, Narelle S Willis^{2,3}, Tess E Cooper³, Jonathan C Craig^{3,4}

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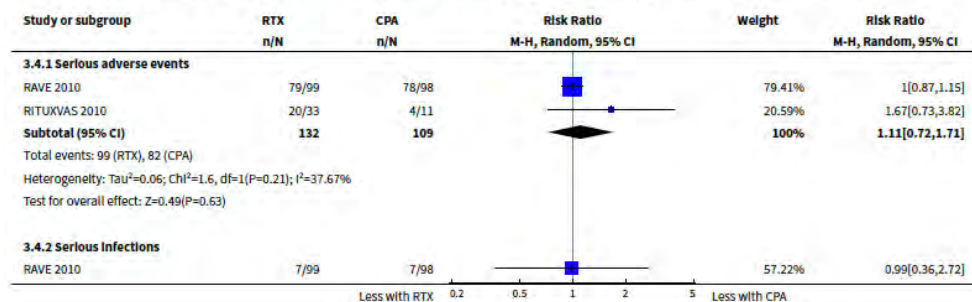
Analysis 3.2. Comparison 3 Rituximab versus cyclophosphamide, Outcome 2 Remission.



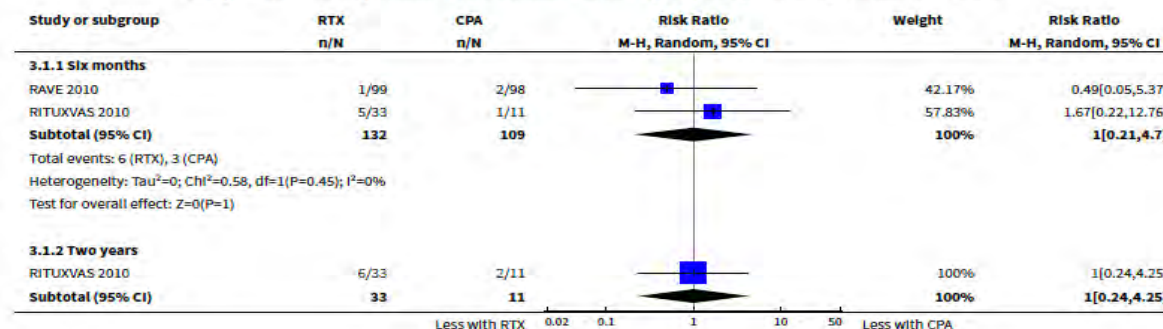
Analysis 3.3. Comparison 3 Rituximab versus cyclophosphamide, Outcome 3 Relapse.



Analysis 3.4. Comparison 3 Rituximab versus cyclophosphamide, Outcome 4 Adverse events.



Analysis 3.1. Comparison 3 Rituximab versus cyclophosphamide, Outcome 1 Death.



- Cyclophosphamide vs Rituximab:
 - Similar rates of remission, relapse, adverse events and death

Clinical outcomes of treatment of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis based on ANCA type

Sebastian Unizony,¹ Miguel Villarreal,² Eli M Miloslavsky,¹ Na Lu,¹ Peter A Merkel,³ Robert Spiera,⁴ Philip Seo,⁵ Carol A Langford,⁶ Gary S Hoffman,⁶ CG M Kallenberg,⁷ E William St. Clair,⁸ David Ikle,² Nadia K Tchao,⁹ Linna Ding,¹⁰ Paul Brunetta,¹¹ Hyon K Choi,¹ Paul A Monach,¹² Fernando Fervenza,¹³ John H Stone,¹ Ulrich Specks,¹³ for the RAVE-ITN Research Group

- A post-hoc analysis of RAVE trial showed that:
 - RTX treated patients were more likely to obtain remission in relapsing disease, compared to CYC
 - Patients with PR3-AAV respond better to RTX than to CYC/AZA

Table 2 Treatment outcomes in patients with AAV according to serological and clinicopathological classifications* †

	PR3-AAV			MPO-AAV			GPA			MPA		
	RTX (n=66)	CYC/AZA (n=65)	p Value	RTX (n=33)	CYC/AZA (n=33)	p Value	RTX (n=74)	CYC/AZA (n=74)	p Value	RTX (n=24)	CYC/AZA (n=24)	p Value
CR at 6 months	43 (65)	31(48)	0.04	20 (61)	21 (64)	0.80	46 (63)	37 (50)	0.11	16 (67)	15 (63)	0.76
CR at 12 months	31 (47)	21 (32)	0.09	16 (49)	17 (52)	0.81	33 (45)	27 (37)	0.28	14 (58)	11 (46)	0.39
CR at 18 months	24 (36)	19 (29)	0.39	15 (46)	13 (39)	0.62	27 (37)	23 (31)	0.45	12 (50)	9 (38)	0.38

Rituximab as therapy to induce remission after relapse in ANCA-associated vasculitis

Rona M Smith ^{1,2}, Rachel Bronwen Jones ², Ulrich Specks ³, Simon Bond ⁴, Marianna Nodale ⁴, Reem Aljayyousi ⁵, Jacqueline Andrews ⁶, Annette Bruchfeld ⁷, Brian Camilleri ⁸, Simon Carette ⁹, Chee Kay Cheung ¹⁰, Vimal Derebail ¹¹, Tim Doulton ¹², Lindsay Forbes ¹³, Shouichi Fujimoto ¹⁴, Shunsuke Furuta ¹⁵, Ora Gewurz-Singer ¹⁶, Lorraine Harper ¹⁷, Toshiko Ito-Ihara ¹⁸, Nader Khalidi ¹⁹, Rainer Klocke ²⁰, Curry Koenig ²¹, Yoshinori Komagata ²², Carol Langford ²³, Peter Lanyon ²⁴, Raashid Ahmed Lugmani ²⁵, Hirofumi Makino ²⁶, Carole McAlear ²⁷, Paul Monach ²⁸, Larry W Moreland ²⁹, Kim Mynard ², Patrick Nachman ¹¹, Christian Pagnoux ³⁰, Fiona Pearce ³¹, Chen Au Peh ³², Charles Pusey ³³, Dwarakanathan Ranganathan ³⁴, Rennie L Rhee ³⁵, Robert Spiera ³⁶, Antoine G Sreih ³⁷, Vladimir Tesar ³⁸, Giles Walters ³⁹, Michael H Weisman ¹³, Caroline Wroe ⁴⁰, Peter Merkel ⁴¹, David Jayne ^{1,2}, RITAZAREM coinvestigators

- Results from the open-label induction period of RITAZAREM trial report high rates of remission after RTX induction in relapsing patients

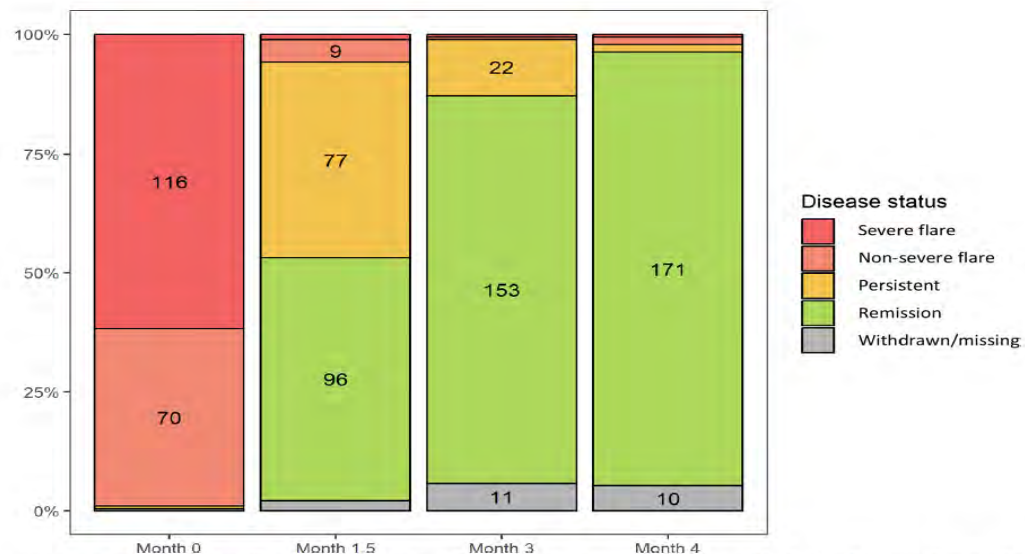


Figure 2 Disease response according to baseline BVAS/WG score. Figures represent the number of individuals according to disease status. In addition to those displayed on the graph: at month 1.5, two individuals had severe disease, and four were withdrawn/missing. At month 3, one individual had severe disease and one limited disease. At month 4, one individual had severe disease, three had limited disease and three had persistent disease. Withdrawn/missing includes all participants who did not attend a study visit either due to death, withdrawal from trial or a missed visit. BVAS/WG, Birmingham Vasculitis Activity Score for Wegener's granulomatosis.

Treatment – GPA/MPA (non-organ/life-threatening)

- For induction of remission of non-organ or non-life-threatening GPA/MPA, treatment with a combination of glucocorticoids and rituximab is recommended.

Level of evidence: 1b
Grade of recommendation: B
Level of agreement: 9.2 ± 0.8

- Methotrexate and mycophenolate mofetil can be considered as alternatives to rituximab

Level of evidence: 1b
Grade of recommendation: B
Level of agreement: 9.2 ± 0.8

Treatment – GPA/MPA (non-organ/life-threatening)

- For induction of remission of non-organ or non-life-threatening GPA/MPA, treatment with a combination of glucocorticoids and rituximab is recommended.

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Grade of recommendation: B
Level of agreement: 9.2 ± 0.8

- Methotrexate and mycophenolate mofetil can be considered as alternatives to rituximab

Level of evidence: 1b
Grade of recommendation: B
Level of agreement: 9.2 ± 0.8

Based on higher doses of glucocorticoids required with MTX and MMF

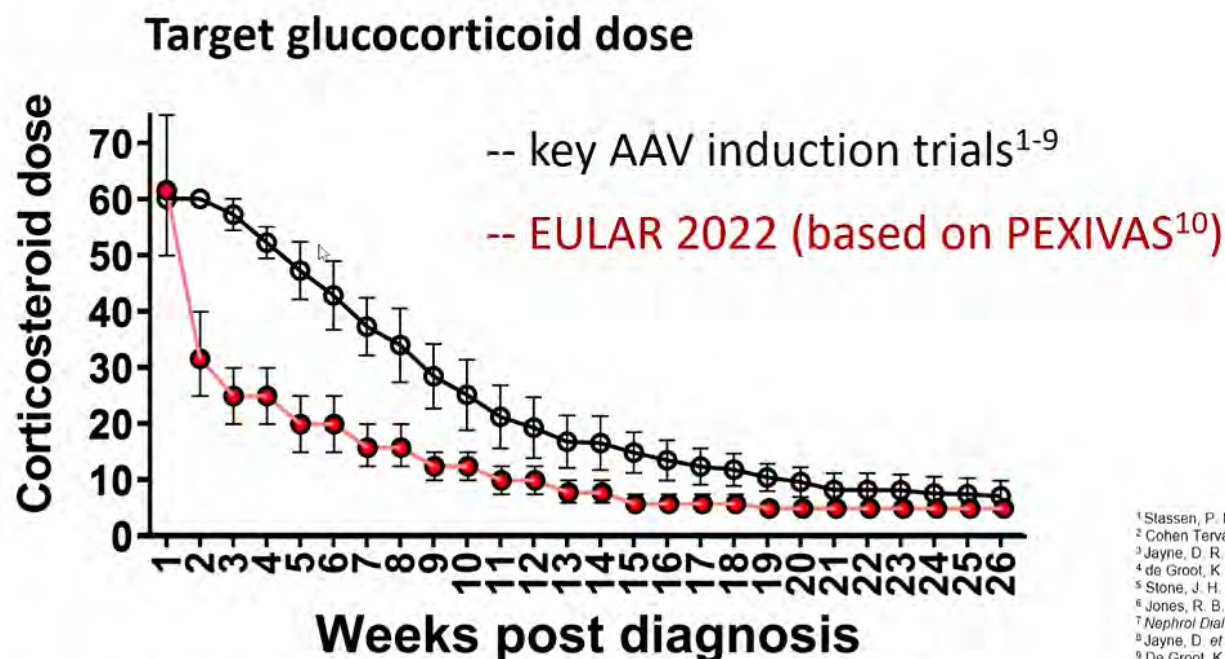
Treatment – GPA/MPA

- As part of regimens for induction of remission in GPA / MPA we recommend treatment with oral glucocorticoids at a starting dose of 50-75 mg prednisolon/day, depending on body weight. We recommend stepwise reduction of glucocorticoids and achieving a dose of 5 mg prednisolone/day by 4-5 months.

Level of evidence: 1b
Grade of recommendation: A
Level of agreement: 9.4 ± 0.8

Treatment – GPA/MPA

- As part of regimens for induction of remission in GPA / MPA we recommend treatment with oral glucocorticoids at a starting dose of 50-75 mg prednisolon/day, depending on body weight. We recommend stepwise reduction of glucocorticoids and achieving a dose of 5 mg prednisolone/day by 4-5 months.



Level of evidence: 1b
Grade of recommendation: A
Level of agreement: 9.4 ± 0.8

Similar efficacy and less adverse events with lower dose of corticosteroids in the PEXIVAS trial

Treatment – GPA/MPA

- Avacopan in combination with rituximab or cyclophosphamide may be considered for induction of remission in GPA/MPA, as part of a strategy to substantially reduce exposure to glucocorticoids.

Level of evidence: 1b

Grade of recommendation: B

Level of agreement: 9.0 ± 0.9

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Avacopan for the Treatment of ANCA-Associated Vasculitis

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AMERICAN COLLEGE
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Empowering Rheumatology Professionals

Adjunctive Treatment With Avacopan, an Oral C5a Receptor Inhibitor, in Patients With Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

Peter A. Merkel,¹  John Niles,² Richard Jimenez,³ Robert F. Spiera,⁴  Brad H. Rovin,⁵ Andrew Bomback,⁶
Christian Pagnoux,⁷ Antonia Potarca,⁸ Thomas J. Schall,⁸ and Pirow Bekker,⁸ for the CLASSIC Investigators

Avacopan enabled a reduced dose of glucocorticoids with similar efficacy and less adverse events, when used together with RTX or CYC

Treatment – GPA/MPA

- Plasma exchange may be considered as part of therapy to induce remission in GPA/MPA for those with a serum creatinine $> 300 \mu\text{mol/L}$ (3.4 mg/dl) due to active glomerulonephritis.

Level of evidence: 1a
Grade of recommendation: B
Level of agreement: 8.0 ± 1.7

- Routine use of plasma exchange to treat diffuse alveolar hemorrhage in GPA/MPA is not recommended.

Level of evidence: 1b
Grade of recommendation: B
Level of agreement: 8.8 ± 1.3

Former recommendations

Organisation and year of publication	Recommendation of plasma exchange (PLEX) in	
	AAV and kidney involvement	AAV and pulmonary haemorrhage
ASFA 2020 ¹⁴	<p><i>For patients with creatinine $\geq 500 \mu\text{mol/L}$: In favour of PLEX as accepted second line therapy alone or as adjuvant; support use of PLEX in select patients with biopsy proven RPGN (strong recommendation based on moderate quality evidence).</i></p> <p><i>For patients with creatinine $< 500 \mu\text{mol/L}$: Optimal role not established, decision should be individualised (weak recommendation based on low or very low quality evidence)</i></p>	Consider PLEX for pulmonary haemorrhage a class I indication (accepted first line therapy) (strong recommendation based on low quality evidence)
KDIGO 2020 ¹⁵	Against routine use of PLEX for patients with GFR $< 50 \text{ mL/min/1.73 m}^2$; PLEX can be considered for more severe presentations (serum creatinine $> 500 \mu\text{mol/L}$, especially if oliguric)	In favour of PLEX for AAV and diffuse alveolar haemorrhage plus hypoxaemia
ARCH 2020 ¹⁶	In favour of PLEX for AAV and rapidly progressive glomerulonephritis	In favour of PLEX for AAV and pulmonary haemorrhage
Japan Research Committee of the Ministry of Health, Labour, and Welfare 2017 ¹⁷	In favour of PLEX for AAV and severe renal impairment	No recommendation
BSR 2017 ¹⁸	In favour of PLEX for AAV and rapidly progressive glomerulonephritis with serum creatinine $> 5.8 \text{ mg/dL}$	Insufficient evidence to support PLEX for AAV presenting with pulmonary haemorrhage, PLEX possibly beneficial
EULAR/ERA-EDTA 2016 ¹⁹	In favour of PLEX for AAV and serum creatinine level $\geq 500 \text{ mmol/L}$ due to rapidly progressive glomerulonephritis in new or relapsing disease	In favour of PLEX for AAV and severe diffuse pulmonary haemorrhage
CanVasc 2016 ²⁰	Against PLEX as first line therapy for AAV and severe renal involvement (GFR $< 50 \text{ mL/min}$). PLEX may be a reasonable adjuvant therapy if patients clinically deteriorate	Against PLEX as first line therapy for AAV and pulmonary haemorrhage. PLEX may be a reasonable adjuvant therapy if patients clinically deteriorate
BSR/BHPR 2014 ²¹	In favour of PLEX for AAV and severe renal failure (serum creatinine $> 500 \text{ mmol/L}$)	In favour of PLEX for AAV and pulmonary haemorrhage

- High cr levels (5.6 mg/dL)
- May or may not be used for DAH

The effects of plasma exchange in patients with ANCA-associated vasculitis: an updated systematic review and meta-analysis

Michael Walsh,^{1,2,3} David Collister,^{3,4} Linan Zeng,^{2,5} Peter A Merkel,⁶ Charles D Pusey,⁷ Gordon Guyatt,^{1,2} Chen Au Peh,^{8,9} Wladimir Szpirt,¹⁰ Toshiko Ito-Hara,^{11,12} David R W Jayne,¹³ on behalf of the Plasma exchange and glucocorticoid dosing for patients with ANCA-associated vasculitis BMJ Rapid Recommendations Group*

- 704 / 1060 (66%) were from the PEXIVAS trial

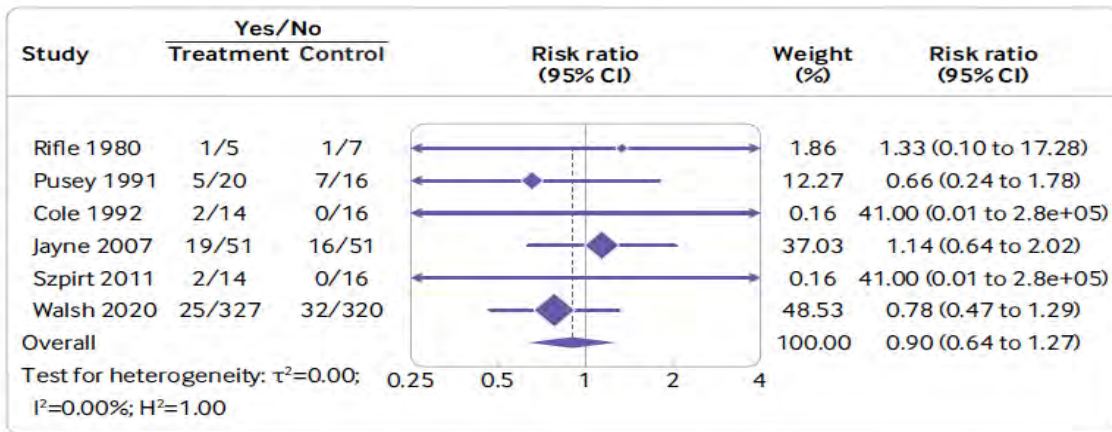
	Values
Trial characteristics	Mean (range) of means across trials
No of patients enrolled	118 (14-704)
Length of follow-up (months)	Median 36 (12-127)
Dose regimen of plasma exchange	Centrifugation or filter separation; 8 trials used albumin and/or crystalloid replacement solution for a median 8 treatments; exchange volume ranged from 1 to 1.5 plasma volumes (or 40 to 60 mL/kg or fixed volume of 3.5-4 L)
Setting	Multiple centres internationally including Europe, North America, and Australasia
Funding	Public funding only (4 trials) In-kind supplies from industry partner (1 trial) Public funding and in-kind supplies from three industry partners (1 trial) Not reported (3 trials)
Patient involvement	No trial reported patient involvement in design or conduct
Patient characteristics	Mean (range) of means across trials
Age (years)	56 (47-67)
Sex (% women)	35 (22-44)
ANCA positive	84% in 6 trials that measured ANCA
Kidney function (serum creatinine concentration $\mu\text{mol/L}$)	Median 716 (256-1176)
Presence of pulmonary haemorrhage	Patients with pulmonary haemorrhage included (4 trials) Patients with severe pulmonary haemorrhage included (1 trial)

RCTs with plasma exchange

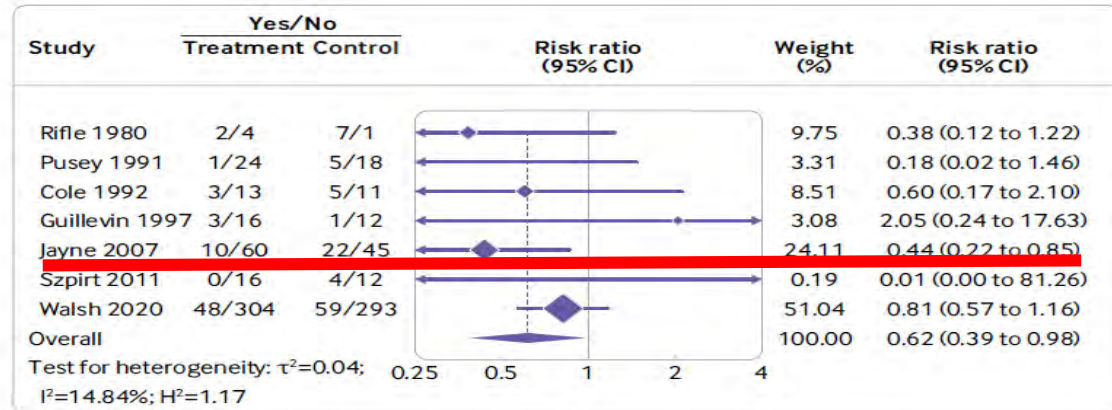
Table 1 | Characteristics of trials of plasma exchange for treatment of ANCA-associated vasculitis and participants included for meta-analysis

Study	Follow-up (months)	Plasma exchange			Participants				Baseline creatinine (µmol/L)		Baseline dialysis (%)		Lung haem	
		Method	No of treatments	Volume/treatment	No	Mean age (years)		Female (%)		PLEX	Ctrl	PLEX		Ctrl
Rifle 1980	22	Centrifuge	5 in 5 days + additional for non-response	1.5 plasma volumes	14	41	52	50	25	893	1140	67	88	No
Mauri 1985	36	Centrifuge and filter	6 in 12 days + additional for non-response	3.5 L	22	NR	NR	NR	NR	1193	1158	50	50	NR
Pusey 1991	58	Centrifuge	5 in 7 days + additional for non-response	4 L	48	52	51	36	39	793	637	44	34	Yes
Cole 1992	12	Centrifuge	≥10 in 16 days	1 plasma volume	32	NR	NR	NR	NR	634	769	25	43	NR
Guillevin 1997	12	Centrifuge and filter	9 or 12 at 3 times/week	60 mL/kg	32	47	62	47	38	439	287	32	15	NR
Zauner 2002	127	NR	3 + <9 for non-response	40 mL/kg	39	55	56	29	22	NR	NR	NR	NR	Yes
Jayne 2007, Walsh 2013	12, 47	Centrifuge and filter	7 in 14 days	60 mL/kg	137	67	66	41	36	701	732	67	71	Yes
Szpirt 2010	60	Filter	6 + 3-6 for persistent ANCA	4 L	32	58	56	25	19	262	250	13	25	Yes
Walsh 2020	35	Centrifuge and filter	7 in 14 days	60 mL/kg	704	63	64	42	45	327	336	19	21	Yes

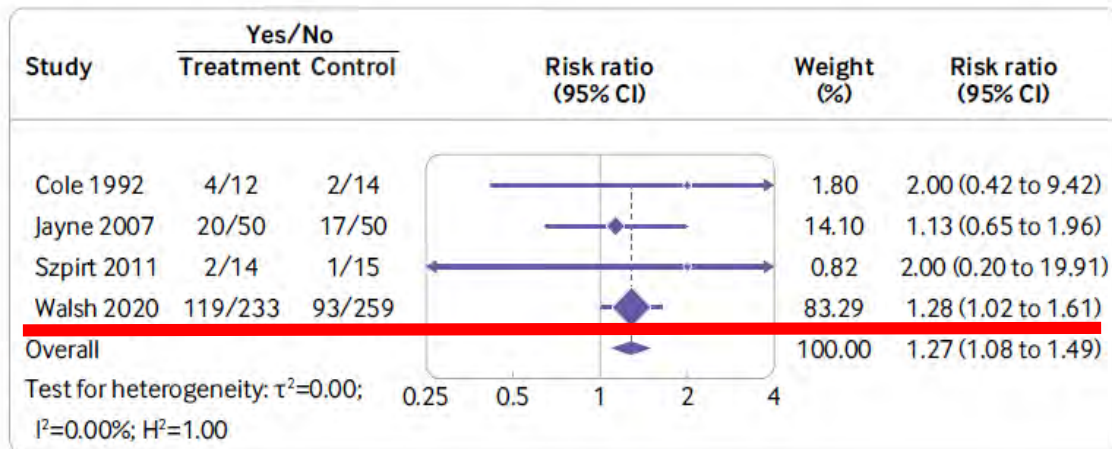
Lung haem = Presence of lung haemorrhage at baseline. PLEX = Plasma exchange. Ctrl = Control. NR = Not reported.



Mortality at month 12



ESRD at month 12



Serious infections at month 12

According to baseline creatinine (<2.3 mg/dL, 2.3-3.4, 3.4-5.8 ve >5.8)

Effects of PLEX by Baseline Disease Severity

Outcome	Risk w/o PLEX	PLEX RR	Risk w/ PLEX	For every 100 pts PLEX you prevent or cause...
ESKD	0.2%	0.62 (0.39 to 0.98)	0.1%	0
	5.0%		3.1%	2
	11.0%		6.8%	4
	38%		23.5%	14
Serious Infection	10%	1.27 (1.08 to 1.49)	12.7	3
	18.0%		22.9	5
	31.5%		40	9
	50.0%		63.5	14

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Treatment – GPA/MPA

- For patients with GPA/MPA with disease **refractory** to therapy to induce remission, we recommend a thorough reassessment of disease status and comorbidities and consideration of options for additional or different treatment. These patients should be managed in close conjunction with or referred to a center with expertise in vasculitis.

Level of evidence: 5

Grade of recommendation: D

Treatment – GPA/MPA

- For **maintenance of remission** of GPA/MPA, after induction of remission with rituximab or cyclophosphamide, we recommend treatment with rituximab.
- Azathioprine or methotrexate may be considered as alternatives.

Level of evidence: 1b

Grade of recommendation: A

Level of agreement: 9.3 ± 1.0

Treatment – GPA/MPA

- We recommend that therapy to maintenance remission for GPA/MPA be continued for 24-48 months following induction remission of new-onset disease.

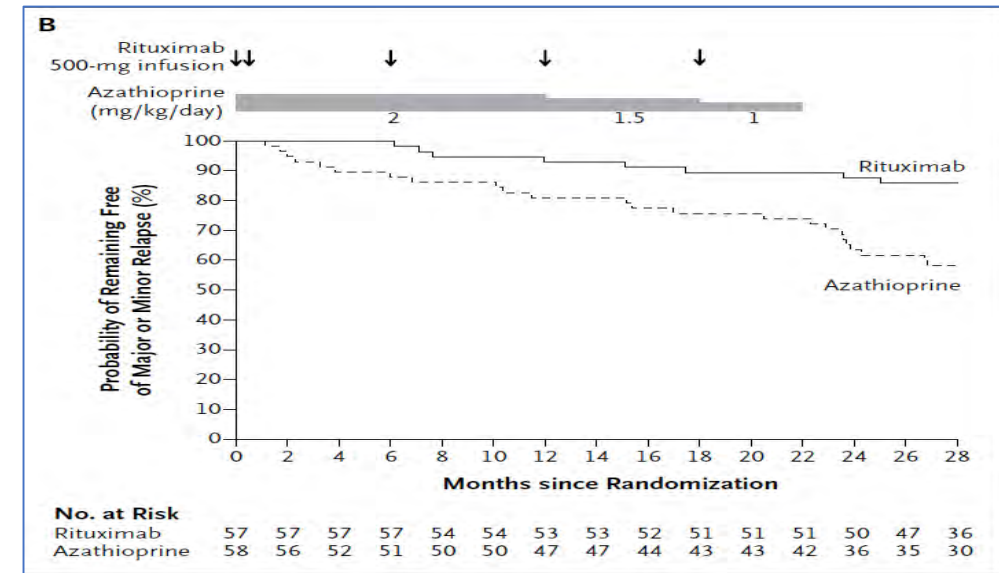
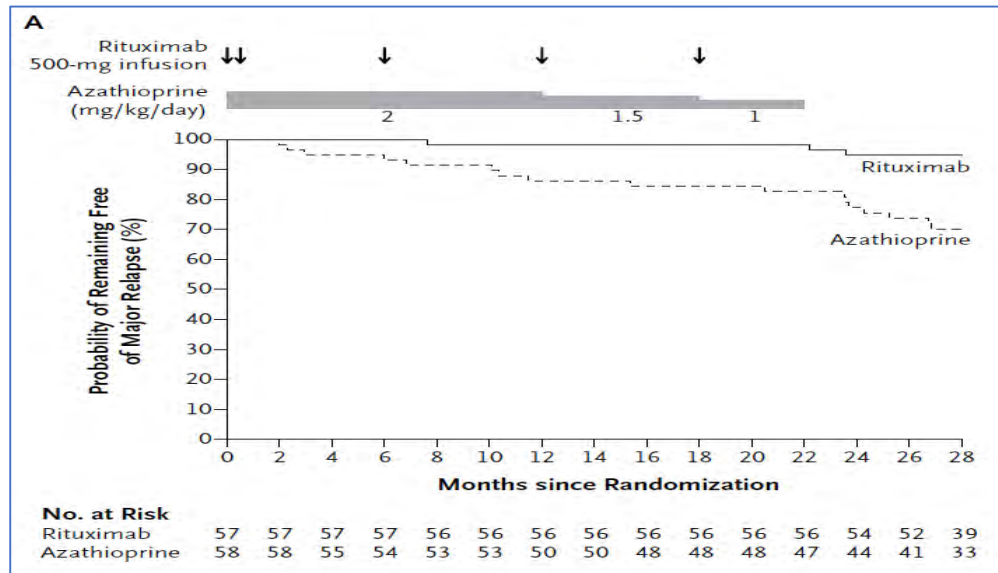
Level of evidence: 1a
Grade of recommendation: B
Level of agreement: 9.1 ± 1.4

- A longer duration therapy should be considered in relapsing patients or those with an increased risk of relapse, but should be balanced against patients preferences and risk of continuing immunosuppression.

Level of evidence: 4
Grade of recommendation: D
Level of agreement: 9.1 ± 1.4

Rituximab versus Azathioprine for Maintenance
in ANCA-Associated Vasculitis

L. Guillevin, C. Pagnoux, A. Karras, C. Khouatra, O. Aumaître, P. Cohen, F. Maurier, O. Decaux, J. Ninet, P. Gobert, T. Quémeneur, C. Blanchard-Delaunay, P. Godmer, X. Puéchal, P.-L. Carron, P.-Y. Hatron, N. Limal, M. Hamidou, M. Ducret, E. Daugas, T. Papo, B. Bonnotte, A. Mahr, P. Ravaud, and L. Mouthon, for the French Vasculitis Study Group*

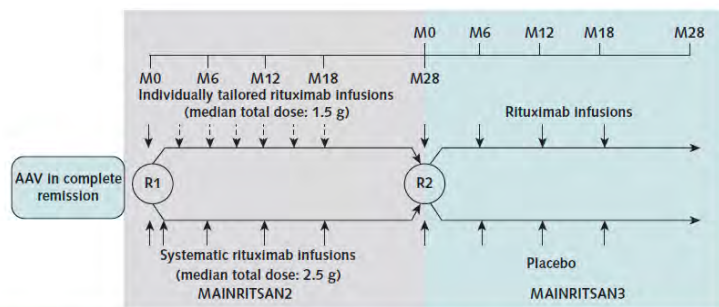


- MAINRITSAN trial showed that more patients remained on sustained remission with RTX compared with AZA at month 28

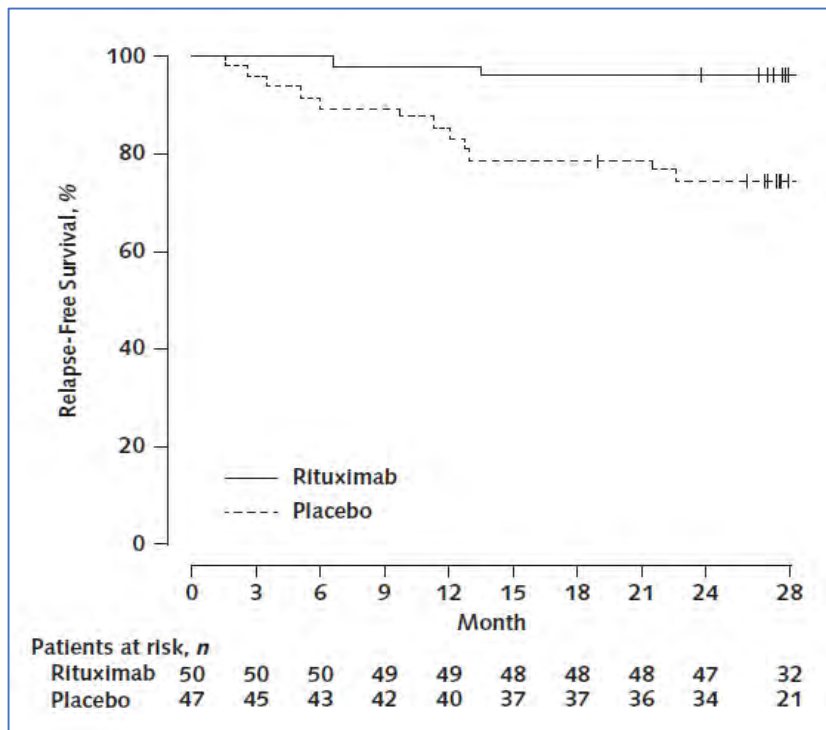
Long-Term Rituximab Use to Maintain Remission of Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

A Randomized Trial

Pierre Charles, MD; Élodie Perrodeau, MSc; Maxime Samson, MD, PhD; Bernard Bonnotte, MD, PhD; Antoine Néel, MD, PhD; Christian Agard, MD, PhD; Antoine Huart, MD; Alexandre Karras, MD, PhD; François Lifermann, MD; Pascal Godmer, MD; Pascal Cohen, MD; Catherine Hanrotel-Saliou, MD; Nicolas Martin-Silva, MD; Grégory Pugnet, MD, PhD; François Maurier, MD; Jean Sibilia, MD, PhD; Pierre-Louis Carron, MD; Pierre Gobert, MD; Nadine Meaux-Ruault, MD; Thomas Le Gallou, MD; Stéphane Vinzio, MD; Jean-François Viillard, MD, PhD; Eric Hachulla, MD, PhD; Christine Vinter, MD; Xavier Puéchal, MD, PhD; Benjamin Terrier, MD, PhD; Philippe Ravaud, MD, PhD; Luc Mouthon, MD, PhD; and Loïc Guillevin, MD; for the French Vasculitis Study Group*



The primary end point of MAINRITSAN2 was evaluated after 28 mo of follow-up. At that time, eligible patients were randomly assigned again to MAINRITSAN3 treatment groups and evaluated 28 mo later. In MAINRITSAN2, patients in the individually tailored rituximab group received a 500-mg infusion at M0 and subsequent infusions according to laboratory values (ANCA and circulating CD19⁺ B cells) assessed every 3 mo until M18. Those in the systematic treatment group received a 500-mg infusion on days 0 and 14, then at M6, M12, and M18. In MAINRITSAN3, participants received infusions (500 mg of rituximab or placebo) at inclusion, M6, M12, and M18. AAV = ANCA-associated vasculitis; ANCA = antineutrophil cytoplasmic antibody; M = month; MAINRITSAN = Maintenance of Remission Using Rituximab in Systemic ANCA-Associated Vasculitis; R = randomization.



MAINRITSAN3 trial has shown that treatment with biannual RTX over 18 months was associated with less relapses compared with standard treatment

Treatment – EGPA (organ- or life-threatening)

- For induction of remission in patients with new onset or relapsing EGPA with organ or life-threatening manifestations, we recommend treatment with a combination of high-dose glucocorticoids and cyclophosphamide.
- A combination of high-dose glucocorticoids and rituximab may be considered as an alternative

Level of evidence: 2b

Grade of recommendation: B

Level of agreement: 9.6 ± 0.8

Treatment – EGPA (non-organ/life-threatening)

- For remission induction in new onset or relapsing EGPA without organ or life-threatening manifestations we recommend treatment with glucocorticoids.

Level of evidence: 1b

Grade of recommendation: B

Level of agreement: 9.3 ± 0.9

Adding Azathioprine to Remission-Induction Glucocorticoids for Eosinophilic Granulomatosis With Polyangiitis (Churg-Strauss), Microscopic Polyangiitis, or Polyarteritis Nodosa Without Poor Prognosis Factors

A Randomized, Controlled Trial

Xavier Puéchal,¹ Christian Pagnoux,¹ Gabriel Baron,² Thomas Quémeneur,³ Antoine Néel,⁴ Christian Agard,⁴ François Lifermann,⁵ Eric Liozon,⁶ Marc Ruivard,⁷ Pascal Godmer,⁸ Nicolas Limal,⁹ Arsène Mékinian,¹⁰ Thomas Papo,¹¹ Anne-Marie Ruppert,¹² Anne Bourgarit,¹³ Boris Bienvenu,¹⁴ Loïck Geffray,¹⁵ Jean-Luc Saraux,¹⁶ Elisabeth Diot,¹⁷ Bruno Crestani,¹¹ Xavier Delbrel,¹⁸ Laurent Sailler,¹⁹ Pascal Cohen,¹ Véronique Le Guern,¹ Benjamin Terrier,¹ Matthieu Groh,¹ Claire Le Jeunne,¹ Luc Mouthon,¹ Philippe Ravaud,² and Loïc Guillevin,¹ for the French Vasculitis Study Group

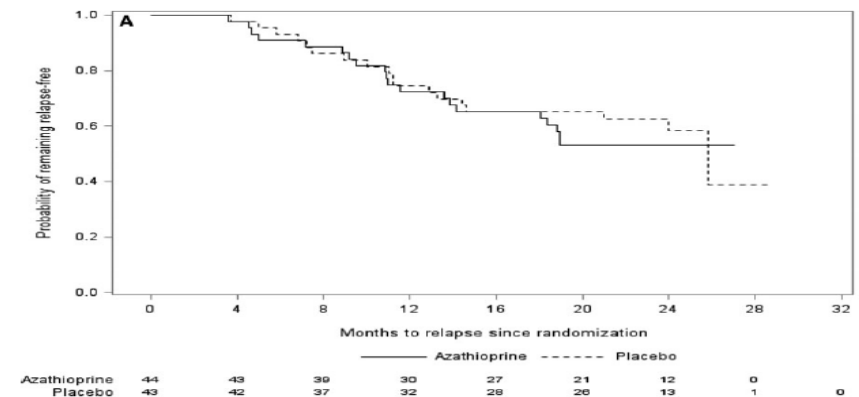


Table 2. Primary and secondary outcomes in the AZA and placebo arms*

Outcome	AZA (n = 46)	Placebo (n = 49)	OR or mean difference (95% CI)
Primary end point: remission induction failures and relapses at month 24†			
Primary analysis	22/46 (47.8)	24/49 (49)	1.08 (0.46, 2.52)‡
Sensitivity analysis	26/50 (52)	25/50 (50)	1.18 (0.52, 2.68)‡
Secondary outcome			
Initial remission	44/46 (95.7)	43/49 (87.8)	2.71 (0.44, 16.71)‡
Minor relapses	13/43 (30.2)	12/42 (28.6)	1.31 (0.51, 3.36)‡§
Major relapses	5/43 (11.6)	5/42 (11.9)	1.28 (0.37, 4.39)‡§
Unclassified relapses	1/43 (2.3)	0/42 (0)	
Any relapses (minor, major, or unclassified)	19/43 (44.2)	17/42 (40.5)	1.28 (0.52, 3.13)‡¶
Deaths	0/46 (0)	2/49 (4.1)	NA
BVAS, mean difference (95% CI)#	-12.4 (-14.0, -10.9)	-12.5 (-14.0, -11.0)	0.1 (-1.1, 1.2)**
HAQ, mean difference (95% CI)#	-0.3 (-0.7, 0.0)	-0.4 (-0.7, -0.1)	0.1 (-0.4, 0.6)**
SF-36			
Physical component score, mean difference (95% CI)#	7.3 (1.5, 13.1)	16.7 (12.5, 21.0)††	-9.5 (-16.4, 2.5)**
Mental component score, mean difference (95% CI)#	3.2 (-2.2, 8.7)	7.5 (2.6, 12.1)	-4.3 (-10.8, 2.3)**
IADL, mean difference (95% CI)#	-0.5 (-5.0, 4.0)	-1.4 (-5.1, 2.3)	0.9 (-5.1, 6.9)**
VDI (month 24), mean difference (95% CI)	1.5 (0.1, 2.8)	1.2 (0.0, 2.5)	0.3 (-0.3, 0.9)**

- In low risk patients (FFS = 0) adding AZA to glucocorticoids did not improve the outcome compared to glucocorticoids alone

Treatment – EGPA (non-organ/life-threatening)

- In patients with **relapsing or refractory** EGPA without active organ- or life-threatening disease, we recommend the use of mepolizumab.

Level of evidence: 1b

Grade of recommendation: B

Level of agreement: 8.9 ± 1.3

Treatment – EGPA

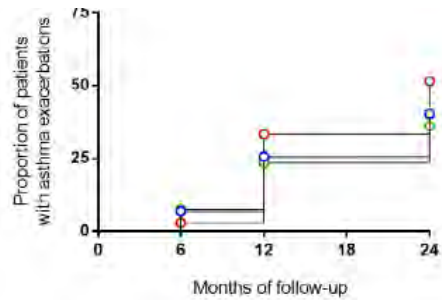
- For **maintenance of remission** of EGPA, after induction of remission for organ- or life-threatening disease, treatment with methotrexate, azathioprine, mepolizumab, or rituximab should be considered.

Level of evidence: 2b, 4
Grade of recommendation: D
Level of agreement: 8.8 ± 1.5

- For maintenance of remission of **relapsing** EGPA, after induction of remission for non-organ- or non-life-threatening manifestations at the time of relapse, we recommend treatment with mepolizumab.

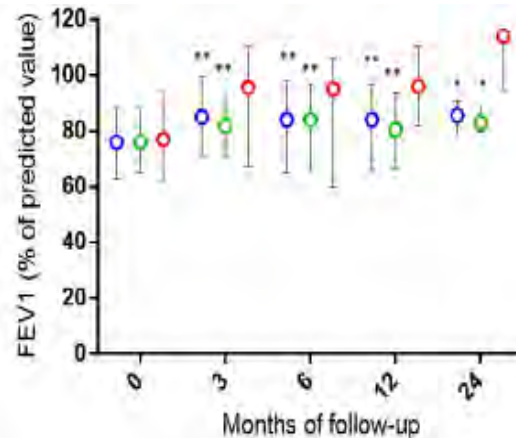
Level of evidence: 1b
Grade of recommendation: B
Level of agreement: 8.8 ± 1.5

Mepolizumab for Eosinophilic Granulomatosis With Polyangiitis: A European Multicenter Observational Study

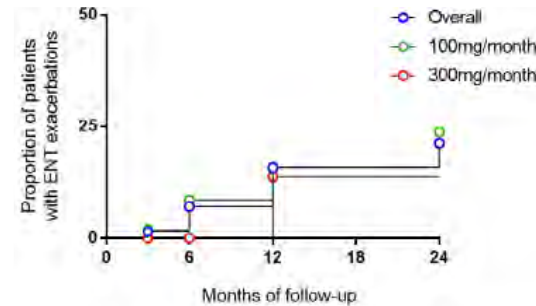


N asthma exacerbations	T6	T12	T24
Overall	14	52	82
100mg	12	37	57
300mg	1	11	17

Asthma exacerbations

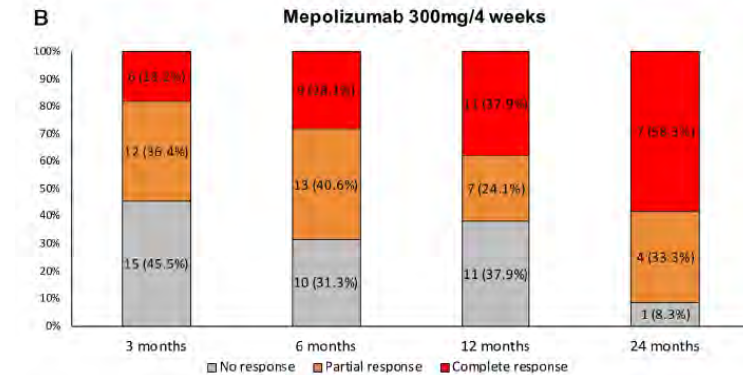
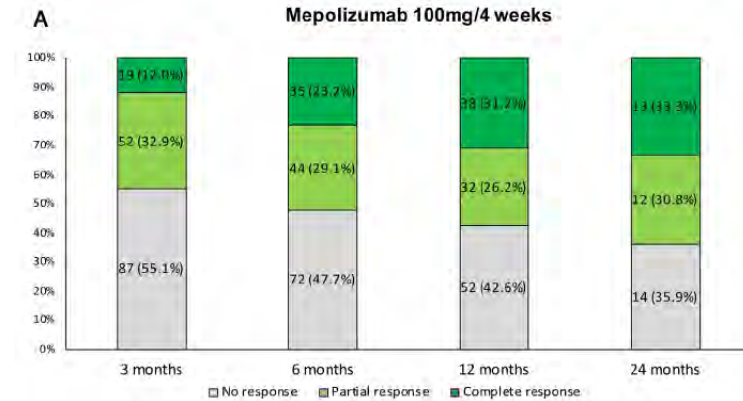


FEV1



N ENT exacerbations	T3	T6	T12	T24
Overall	3	14	28	31
100mg	3	13	22	25
300mg	0	0	4	4

ENT exacerbations



- Both 100 mg/4 weeks and 300 mg/4 weeks were effective
- Significantly reduced BVAS, prednisolone need and eosinophil counts
- Sustained remission rates over 24 months

Biomarkers

- In the management of patients with AAV we recommend that structured clinical assessment, rather than ANCA and/or CD19+ B cell testing alone, should inform decisions on changes in treatment.

Level of evidence: 1b

Grade of recommendation: B

Level of agreement: 9.3 ± 1.1

Immunoglobulins

- In patients with AAV receiving rituximab we recommend measurement of serum immunoglobulin concentrations prior to each course of rituximab to detect secondary immunodeficiency.

Level of evidence: 1b

Grade of recommendation: B

Level of agreement: 9.2 ± 1.4

PJP / Infection prophylaxis

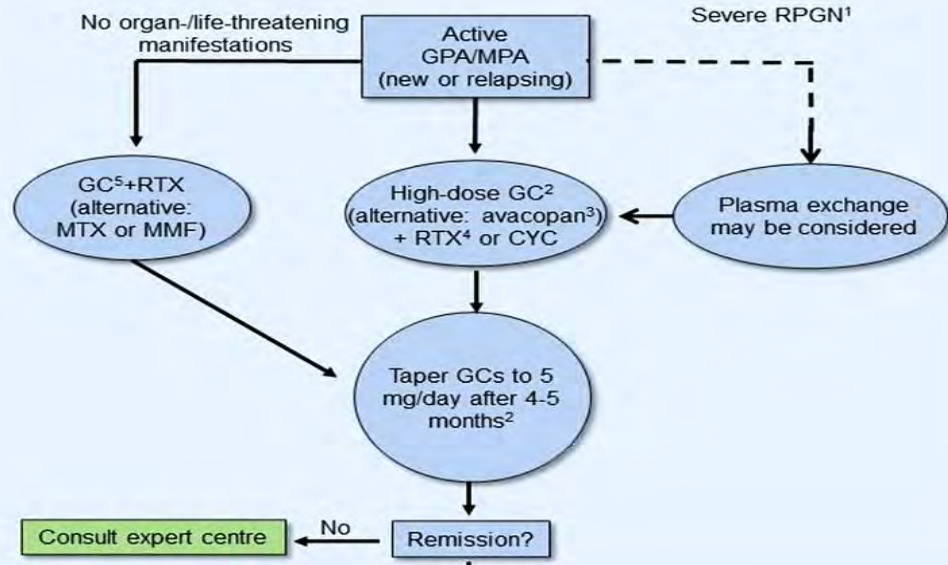
- For patients with AAV receiving rituximab, cyclophosphamide and/or high dose glucocorticoids we recommend the use of trimetoprim-sulfamethoxazole as prophylaxis against pneumocystis jirovecii pneumonia and other infections.

Level of evidence: 3b

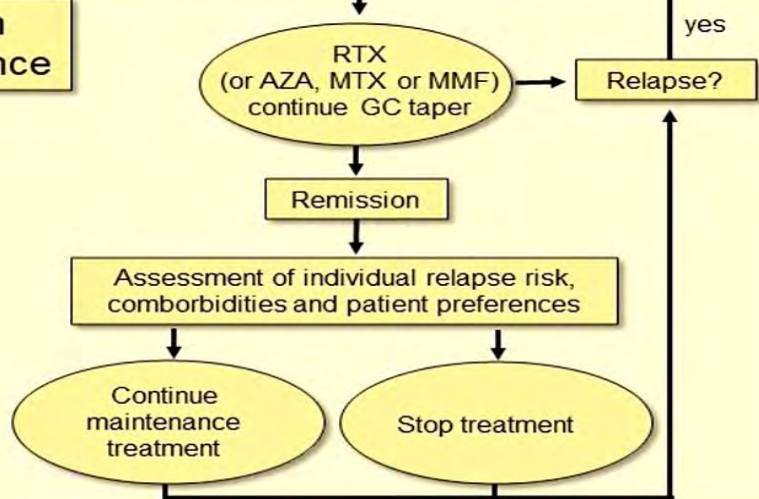
Grade of recommendation: B

Level of agreement: 9.5 ± 1.1

Remission Induction

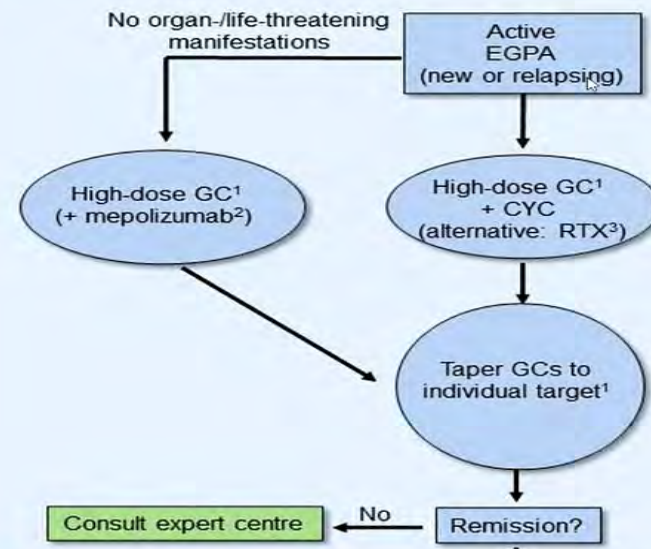


Remission Maintenance

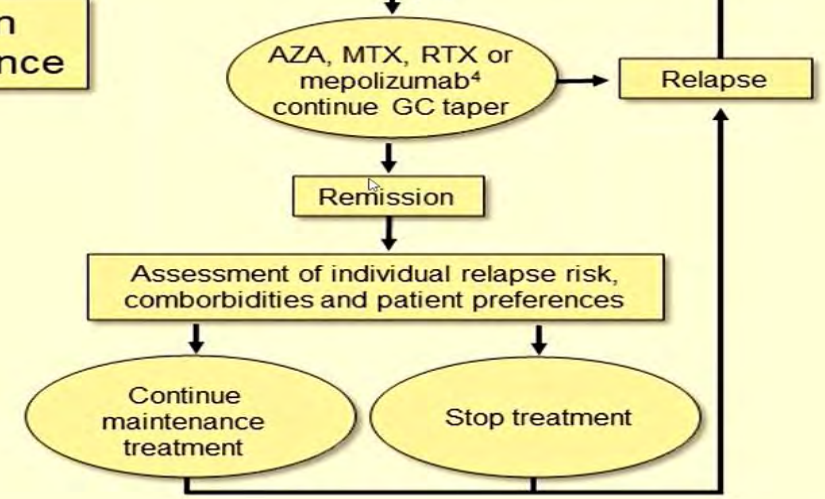


GPA / MPA

Remission Induction



Remission Maintenance



EGPA

2022 ACR/EULAR Classification Criteria for GPA

CLINICAL CRITERIA

Nasal involvement: bloody discharge, ulcers, crusting, congestion, blockage, or septal defect / perforation	+3
Cartilaginous involvement (inflammation of ear or nose cartilage, hoarse voice or stridor, endobronchial involvement, or saddle nose deformity)	+2
Conductive or sensorineural hearing loss	+1

LABORATORY, IMAGING, AND BIOPSY CRITERIA

Positive test for cytoplasmic antineutrophil cytoplasmic antibodies (cANCA) or antiproteinase 3 (anti-PR3) antibodies	+5
Pulmonary nodules, mass, or cavitation on chest imaging	+2
Granuloma, extravascular granulomatous inflammation, or giant cells on biopsy	+2
Inflammation, consolidation, or effusion of the nasal/paranasal sinuses, or mastoiditis on imaging	+1
Pauci-immune glomerulonephritis on biopsy	+1
Positive test for perinuclear antineutrophil cytoplasmic antibodies (pANCA) or antimyeloperoxidase (anti-MPO) antibodies	-1
Blood eosinophil count $\geq 1 \times 10^9$ /liter	-4

- **A score of ≥ 5 is required**
- A diagnosis of small/medium vessel vasculitis should be made
- Mimicks should be excluded

2022 ACR/EULAR Classification Criteria for MPA

CLINICAL CRITERIA

Nasal involvement: bloody discharge, ulcers, crusting, congestion, blockage or septal defect / perforation	-3
--	----

LABORATORY, IMAGING, AND BIOPSY CRITERIA

Positive test for perinuclear antineutrophil cytoplasmic antibodies (pANCA) or antimyeloperoxidase (anti-MPO) antibodies ANCA positive	+6
--	----

Fibrosis or interstitial lung disease on chest imaging	+3
--	----

Pauci-immune glomerulonephritis on biopsy	+3
---	----

Positive test for cytoplasmic antineutrophil cytoplasmic antibodies (cANCA) or antiproteinase 3 (anti-PR3) antibodies	-1
---	----

Blood eosinophil count $\geq 1 \times 10^9$ /liter	-4
--	----

- **A score of ≥ 5 is required**
- A diagnosis of small/medium vessel vasculitis should be made
- Mimicks should be excluded

2022 ACR/EULAR Classification Criteria for EGPA

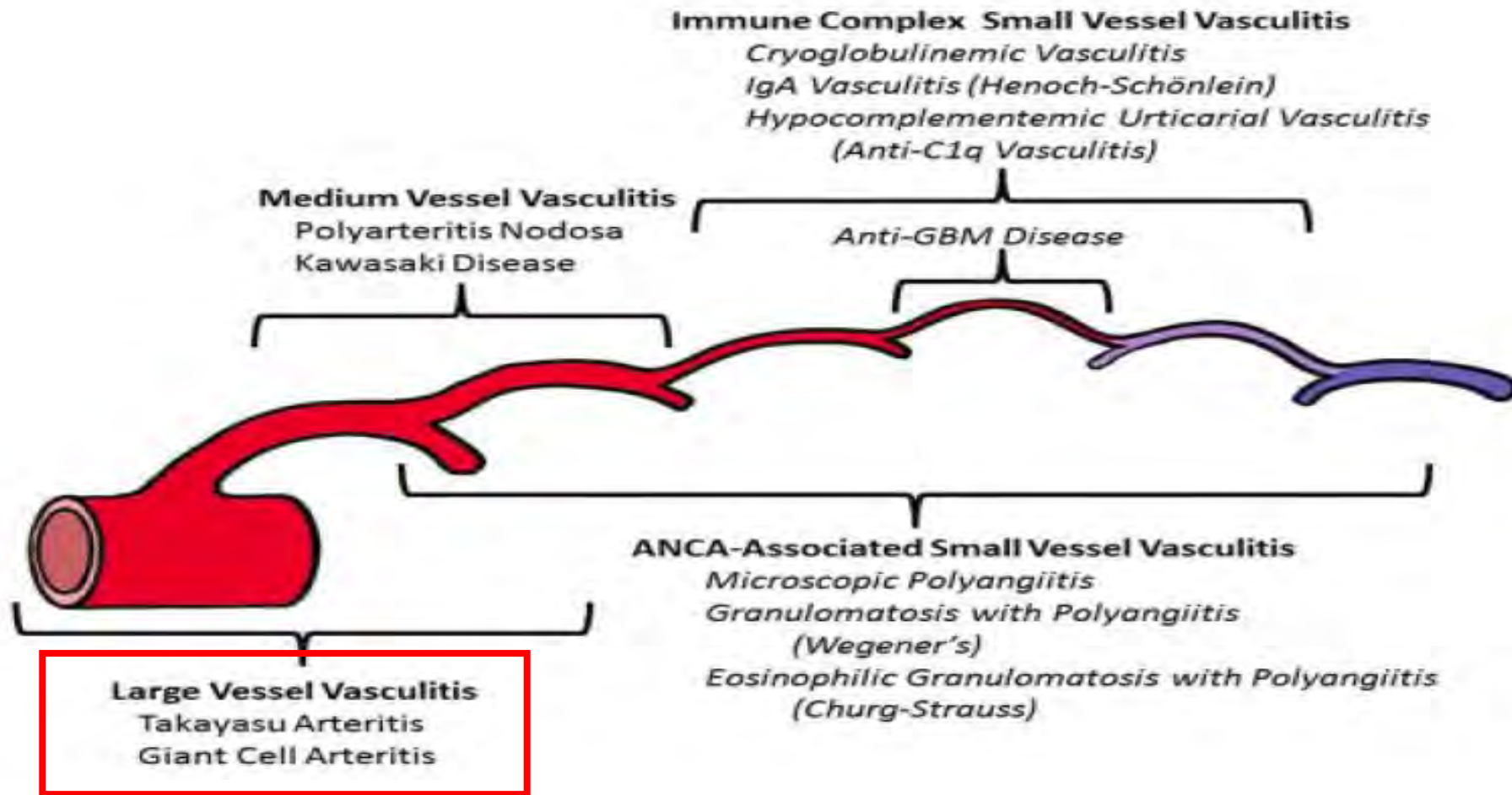
CLINICAL CRITERIA

Obstructive airway disease	+3
Nasal polyps	+3
Mononeuritis multiplex	+1

LABORATORY AND BIOPSY CRITERIA

Blood eosinophil count $\geq 1 \times 10^9$ /liter	+5
Extravascular eosinophilic-predominant inflammation on biopsy	+2
Positive test for cytoplasmic antineutrophil cytoplasmic antibodies (cANCA) or antiproteinase 3 (anti-PR3) antibodies	-3
Hematuria	-1

- **A score of ≥ 6 is required**
- A diagnosis of small/medium vessel vasculitis should be made
- Mimicks should be excluded

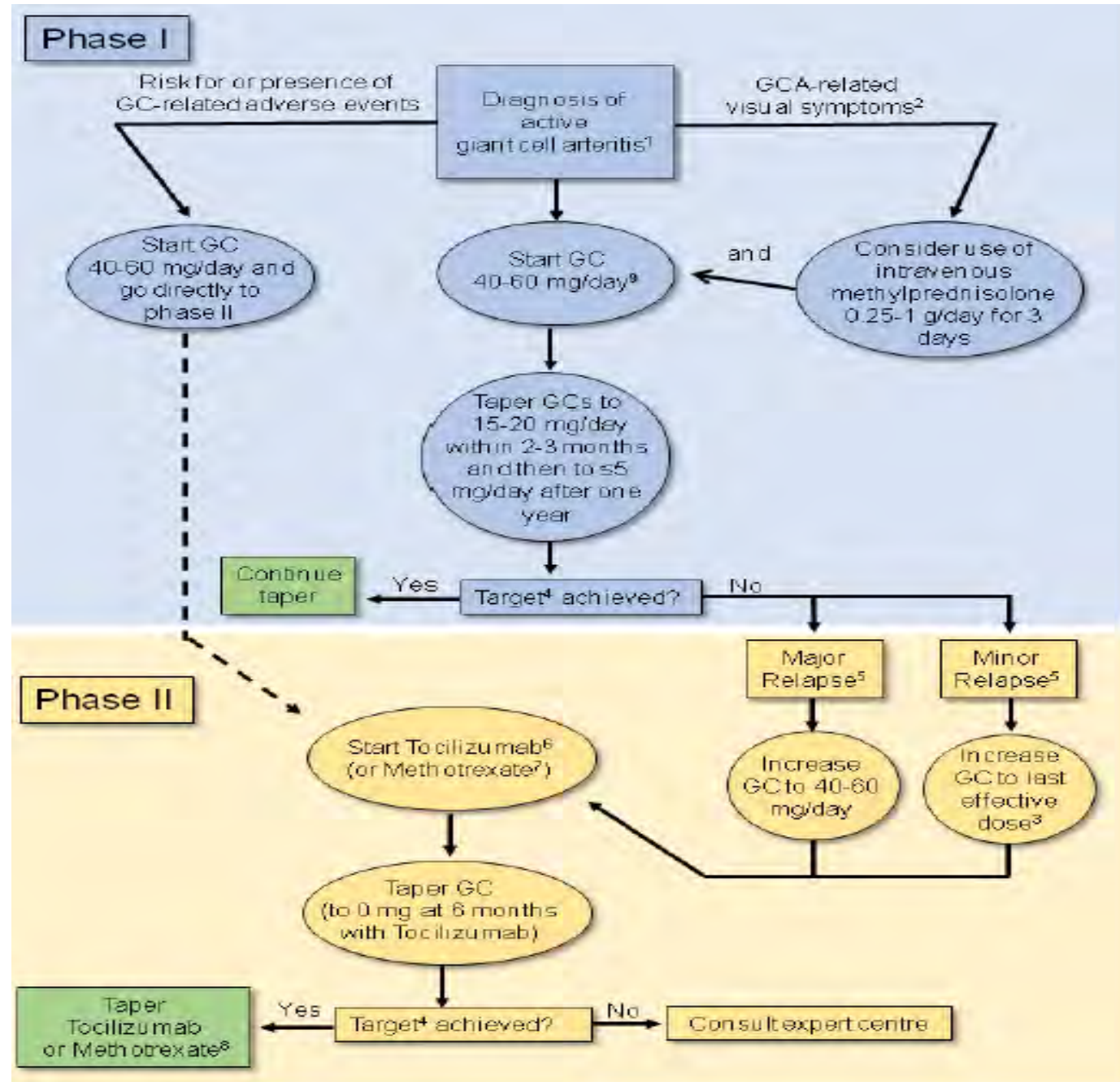


- New real-life data on the optimal use of tocilizumab for GCA
- Leflunomide vs tofacitinib for Takayasu arteritis

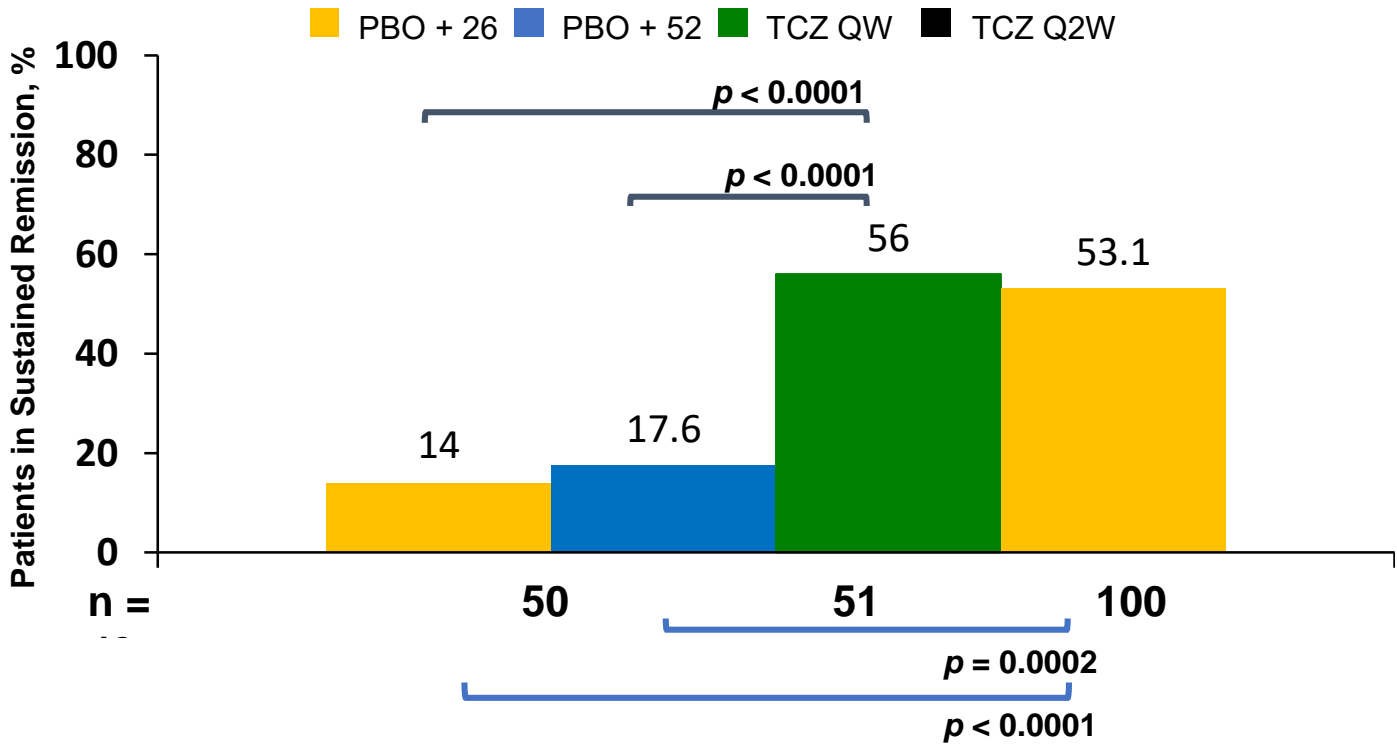
2018 Update of the EULAR recommendations for the management of large vessel vasculitis

Bernhard Hellmich¹, Ana Agueda², Sara Monti³, Frank Buttgereit⁴, Hubert de Booysson⁵, Elisabeth Brouwer⁶, Rebecca Cassie⁷, Maria C Cid⁸, Bhaskar Dasgupta⁹, Christian Dejaco^{10,11}, Gulen Hatemi¹², Nicole Hollinger¹³, Alfred Mahr¹⁴, Susan P Mollan^{15,16}, Chetan Mukhtyar¹⁷, Cristina Ponte^{18,19}, Carlo Salvarani²⁰, Rajappa Sivakumar²¹, Xinping Tian²², Gunnar Tomasson²³, Carl Turesson²⁴, Wolfgang Schmidt²⁵, Peter M Villiger²⁶, Richard Watts²⁷, Chris Young²⁸, Raashid Ahmed Luqmani²⁹

Management of Giant Cell Arteritis

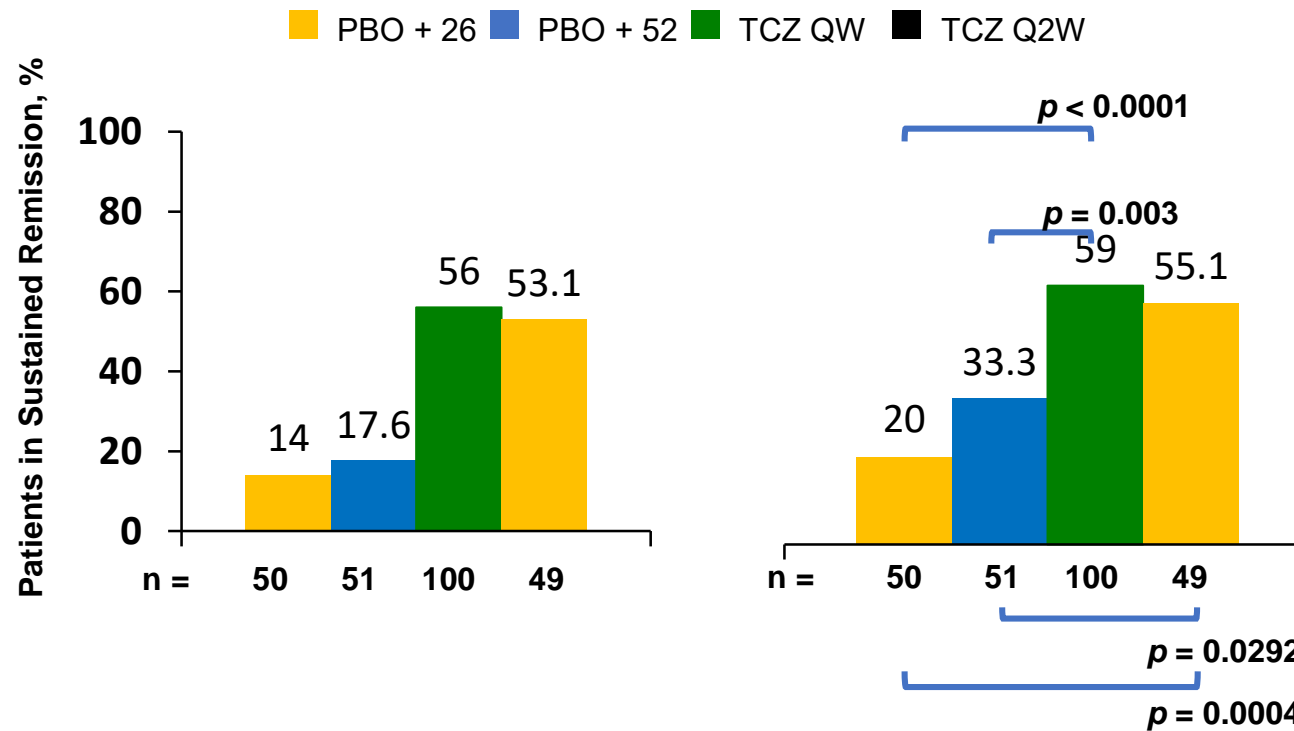


Sustained remission at week 52 without glucocorticoids

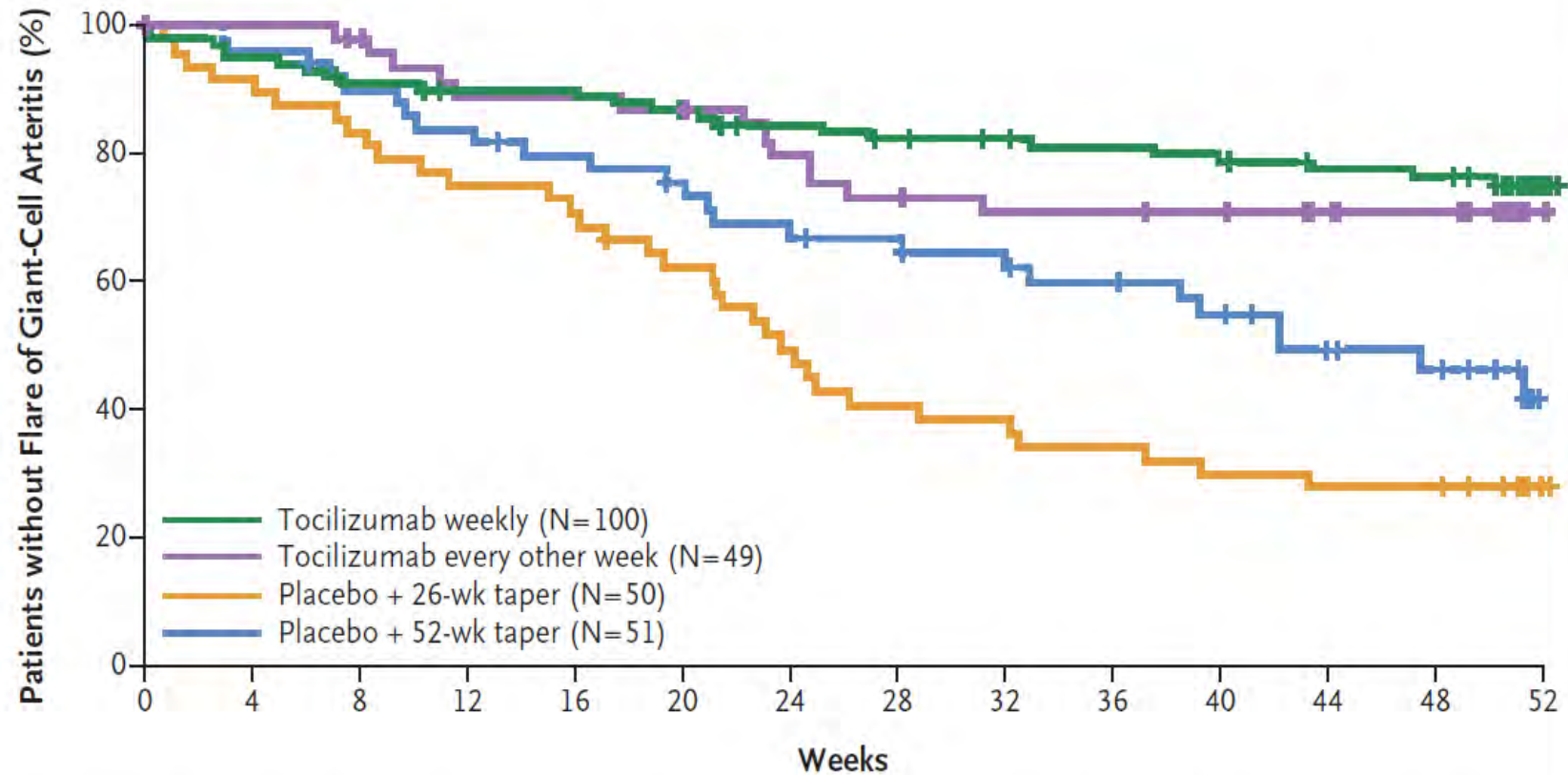


4
5

The results were still robust when CRP was removed the definition of remission



Time to first flare after clinical remission



No. at Risk

Tocilizumab weekly	100	93	88	85	85	81	77	74	71	69	67	64	63	5
Tocilizumab every other week	49	47	45	40	40	39	35	32	30	30	29	26	24	2
Placebo + 26-wk taper	50	44	40	36	34	29	23	19	18	16	14	13	13	3
Placebo + 52-wk taper	51	48	44	41	38	35	32	30	28	25	22	17	15	0

Figure 2. Time to First Flare after Clinical Remission of Giant-Cell Arteritis in All Patients.

TOCILIZUMAB IN NEWLY DIAGNOSED GIANT CELL ARTERITIS VERSUS REFRACTORY/RECURRENT GIANT CELL ARTERITIS: A MULTICENTER STUDY OF 471 PATIENTS OF CLINICAL PRACTICE



Julio Sánchez-Martín¹, Javier Loricera¹, Clara Moriano², Santos Castañeda³, Javier Narváez⁴, Vicente Aldasoro⁵, Olga Maiz⁶, Rafael Melero⁷, Juan I. Villa⁸, Paloma Vela⁹, Susana Romero-Yuste¹⁰, José L. Callejas¹¹, Eugenio Agirregoikoa¹³, Francisca Sivera¹⁴, Jesús C. Fernández-López¹⁵, Carles Galisteo¹⁶, Iván Ferraz-Amaro¹⁷, Lara Sánchez-Bilbao¹, Mónica Calderón-Goercke¹, José L. Hernández¹, Miguel A. González-Gay^{1,19} and Ricardo Blanco¹ on behalf of the Arteritis Spanish Collaborative Group.

¹Department of Rheumatology and Internal Medicine, Hospital Universitario Marqués de Valdecilla, IDIVAL, University of Cantabria, Santander, Spain. ²Department of Rheumatology, Complejo Asistencial Universitario de León, León, Spain. ³Department of Rheumatology, Hospital Universitario de La Princesa, IIS-Princesa, Catedra UAM-Roche, EPID-Future, UAM, Madrid, Spain. ⁴Department of Rheumatology, Hospital de Bellvitge, Barcelona, Spain. ⁵Department of Rheumatology, Complejo Hospitalario de Navarra, Pamplona, Spain. ⁶Department of Rheumatology, Hospital Universitario de Donostia, San Sebastián, España. ⁷Department of Rheumatology, Complejo Hospitalario Universitario de Vigo, Vigo, Spain. ⁸Department of Rheumatology, Hospital Sierrallana, Torrelavega, Spain. ⁹Department of Rheumatology, Hospital General Universitario de Alicante, Alicante, Spain. ¹⁰Department of Rheumatology, Complejo Hospitalario Universitario de Pontevedra, Pontevedra, Spain. ¹¹Department of Rheumatology, Hospital San Cecilio, Granada, Spain. ¹²Department of Rheumatology, Hospital La Paz, Madrid, Spain. ¹³Department of Rheumatology, Hospital de Basurto, Bilbao, Spain. ¹⁴Department of Rheumatology, Hospital Universitario de Elda, Alicante, Spain. ¹⁵Department of Rheumatology, Hospital Universitario Juan Canalejo, A Coruña, Spain. ¹⁶Department of Rheumatology, Hospital Parc Taulí, Barcelona, Spain. ¹⁷Department of Rheumatology, Complejo Hospitalario Universitario de Canarias, Tenerife, Spain. ¹⁸Department of Rheumatology, Hospital Universitario 12 de Octubre, Madrid, Spain. ¹⁹Cardiovascular Pathophysiology and Genomics Research Unit, School of Physiology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa.

Background

Tocilizumab (TCZ) is the only biologic drug approved in giant cell arteritis (GCA), based in two clinical trials (CT) (1,2). CT included selected patients who may differ from those of clinical practice (CP). A high proportion of GCA patients treated with TCZ in CT had a newly diagnosed GCA, whereas in CP, most of them are refractory/recurrent GCA (3,4). Although in CT the efficacy of TCZ seems to be similar in patients with newly diagnosed GCA and in patients with refractory/recurrent GCA, in CP it is not documented.

Objective

To compare in CP, the effectiveness and safety of TCZ in newly diagnosed vs refractory/recurrent GCA.

Methods

Multicentre observational study on 471 GCA patients treated with TCZ. GCA was diagnosed by: a) ACR criteria, and/or b) temporal artery biopsy, and/or c) imaging techniques. A comparative study between patients with newly diagnosed GCA (<6 weeks) and those with refractory/recurrent GCA (>6 weeks) (according to GiACTA study definitions) (2). Sustained remission was based on EULAR definitions (5).

TABLE. Main features of patients with newly diagnosed GCA and refractory/recurrent GCA treated with tocilizumab.

	Newly diagnosed GCA (n=91)	Refractory/recurrent GCA (n=380)	P
Baseline characteristics at TCZ onset			
Age(years), meanSD	74.38.5	73.39.1	0.35
Sex, female/male (% female)	60/31 (66)	282/98 (74)	0.11
Time from GCA diagnosis to TCZ onset (months), median [IQR]	1 [0.5-1]	10 [4-24]	0.0001
ESR, mm 1st hour, median [IQR]	46 [17.5-80.5]	27 [10-50]	0.02
CRP, mg/dL, median [IQR]	2.1 [0.7-8.5]	1.3 [0.4-2.8]	0.13
Haemoglobin, g/dL, meanSD	12.31.5	12.71.5	0.03
Prednisone dose, mg/day, median [IQR]	40 [21.2-50]	15 [10-30]	<0.001
Effectiveness and Safety after TCZ onset			
Follow-up, (months), median [IQR]	15 [5-27.5]	22 [11-37]	0.004
Relevant adverse events, n (%)	23 (25)	102 (27)	0.54
Relevant adverse events per 100 patients-year	20	15	NS
Serious infections, n (%)	13 (14)	53 (14)	0.49
Serious infections per 100 patients-year	11.2	8	NS
MACES, n (%)	0 (0)	1 (0.3)	-
MACES per 100 patients-year	0	0.2	-
Malignancies n (%)	2 (2)	3 (0.8)	0.99
Malignancies per 100 patients-year	1.6	0.5	NS

Abbreviations: CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; GCA: giant cell arteritis; IQR: interquartile range; IV: intravenous; MACES: major adverse cardiovascular events; NS: non significant; SC: subcutaneous; SD: standard deviation

Results

The 471 GCA patients were divided into 2 subgroups: a) newly diagnosed GCA (n=91) and b) refractory/recurrent GCA (n=380) (TABLE).

No significant differences were observed between both groups in sustained remission, although a greater tendency towards sustained remission is observed in newly diagnosed than in refractory/recurrent GCA patients (FIGURE). The decrease in glucocorticoids dose was faster in the first three months in the newly diagnosed GCA group, but thereafter, was similar in both groups, as well as the appearance of relevant adverse events and serious infections.

Conclusion

The effectiveness and safety of TCZ seems to be similar in patients with newly diagnosed GCA and in patients with refractory/recurrent GCA.

Figure A: Sustained Remission

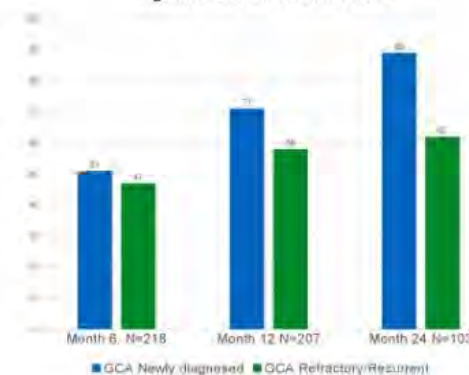
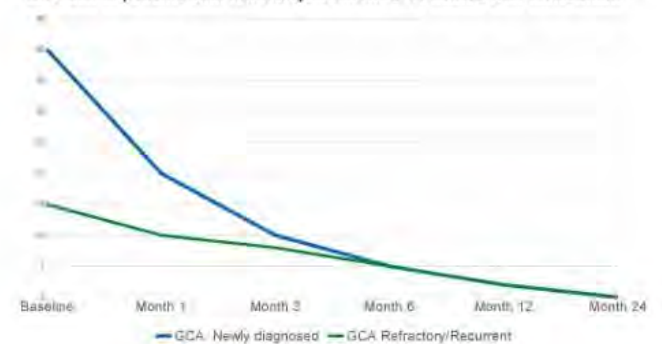


Figure B: median Prednisone dose required in patients with newly diagnosed GCA and in patients with refractory/recurrent GCA treated with tocilizumab



References

- Villiger PM, et al. Lancet. 2016; 387:1921-1927. PMID: 26952547
- Stone JH, et al. N Engl J Med. 2017; 377:317-328. PMID: 28745999
- Calderón-Goercke M, et al. Semin Arthritis Rheum. 2019; 49: 126-135. PMID: 30655091
- Calderón-Goercke M, et al. Clin Exp Rheumatol. 2020; 124: 5112-119. PMID: 32441643
- Hellmich B, et al. Ann Rheum Dis. 2020; 79: 19-30. PMID: 31270110



TOCILIZUMAB IN NEWLY DIAGNOSED GIANT CELL ARTERITIS VERSUS REFRACTORY/RECURRENT GIANT CELL ARTERITIS: A MULTICENTER STUDY OF 471 PATIENTS OF CLINICAL PRACTICE

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Background

Tocilizumab (TCZ) has been approved in two countries for the treatment of selected patients with giant cell arteritis (GCA) of clinical practice. The aim of this study was to compare the efficacy and safety of TCZ in newly diagnosed GCA and in patients with refractory/recurrent GCA, in a multicenter observational study.

Objectives

To compare the efficacy and safety of TCZ in newly diagnosed GCA and in patients with refractory/recurrent GCA.

Methods

Multicentre observational study on 471 GCA patients treated with TCZ. GCA was diagnosed by: a) ACR criteria, and/or b) temporal artery biopsy, and/or c) imaging techniques. A comparative study between patients with newly diagnosed GCA (<6 weeks) and those with refractory/recurrent GCA (>6 weeks) (according to GiACTA study definitions) (2). Sustained remission was based on EULAR definitions (5).

- Multicentre observational study on 471 GCA patients treated with TCZ.
 - Newly diagnosed GCA (n=91)
 - Refractory/recurrent GCA (n=380)
- Similar safety and efficacy

Relevant adverse events, n (%)	23 (25)	102 (27)	0.54
Relevant adverse events per 100 patients-year	20	15	NS
Serious infections, n (%)	13 (14)	53 (14)	0.49
Serious infections per 100 patients-year	11.2	8	NS
MACES, n (%)	0 (0)	1 (0.3)	-
MACES per 100 patients-year	0	0.2	-
Malignancies n (%)	2 (2)	3 (0.8)	0.99
Malignancies per 100 patients-year	1.6	0.5	NS

Abbreviations: CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; GCA: giant cell arteritis; IQR: interquartile range; IV: intravenous; MACES: major adverse cardiovascular events; NS: non significant; SC: subcutaneous; SD: standard deviation

Results

471 GCA patients were divided into 2 subgroups: a) newly diagnosed GCA (n=91) and b) refractory/recurrent GCA (n=380) (TABLE).

Significant differences were observed between both groups in sustained remission, although a clear tendency towards sustained remission is observed in newly diagnosed than in refractory/recurrent GCA patients (FIGURE). The decrease in glucocorticoids dose was faster in the first three months in the newly diagnosed GCA group, but thereafter, was similar in both groups, as well as the appearance of relevant adverse events and serious infections.

Conclusion

The effectiveness and safety of TCZ seems to be similar in patients with newly diagnosed GCA and in patients with refractory/recurrent GCA.

Figure A: Sustained Remission

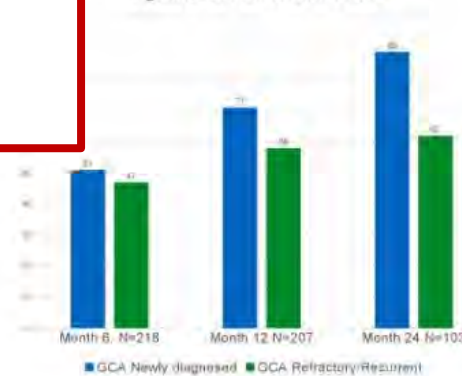
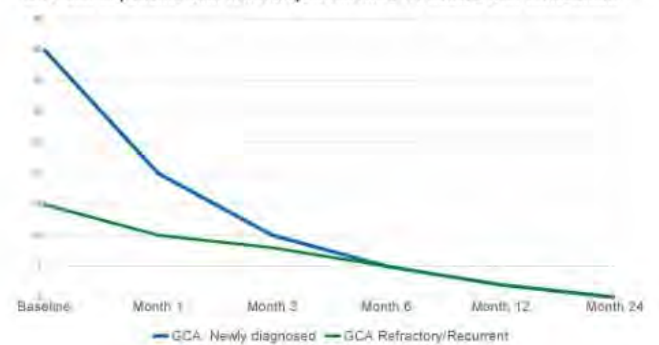


Figure B: median Prednisone dose required in patients with newly diagnosed GCA and in patients with refractory/recurrent GCA treated with tocilizumab



References

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INTRAVENOUS VERSUS SUBCUTANEOUS TOCILIZUMAB IN A SERIES OF 471 PATIENTS WITH GIANT CELL ARTERITIS

Lara Sánchez-Bilbao¹, Javier Loricera¹, Santos Castañeda², Clara Moriano³, Javier Narváez⁴, Vicente Aldasoro⁵, Olga Maiz⁶, Rafael Melero⁷, Juan I. Villa⁸, Paloma Vela⁹, Susana Romero-Yuste¹⁰, José L. Callejas¹¹, Eugenio de Miguel¹², Eva Galíndez-Agirregoikoa¹³, Francisca Sivera¹⁴, Jesús C. Fernández-López¹⁵, Carlos Galisteo¹⁶, Iván Ferraz-Amaro¹⁷, Julio Sánchez-Martín¹⁸, Mónica Calderon-Goercke¹⁹, José L. Hernández²⁰, Miguel A. Gorzález-Gay²¹, and Ricardo Blanco¹ on behalf of the Tocilizumab in Giant Cell Arteritis Spanish Collaborative Group

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BACKGROUND

Tocilizumab (TCZ) has shown efficacy in large-vessel vasculitis, including Giant Cell Arteritis (GCA). Clinical trials with TCZ in GCA was performed with intravenous (iv) TCZ in a phase 2 trial, and with subcutaneous (sc) TCZ in the phase 3 GiACTA. However, in GCA there are no studies comparing IV vs SC TCZ.

OBJECTIVE

To compare the efficacy of TCZ in GCA patients according to the route of administration IV-TCZ vs SC-TCZ.

METHODS

Multicenter study of 471 patients diagnosed with GCA and treated with TCZ. They were divided into 2 groups according to the route of administration: **a)** IV, and **b)** SC. GCA was diagnosed by: **a)** ACR criteria, and/or **b)** temporal artery biopsy, and/or **c)** imaging techniques. Sustained remission was established according to EULAR definitions

RESULTS

We studied 471 patients (mean age, 74±9 years) treated with TCZ, 238 with IV-TCZ and 233 with SC-TCZ (TABLE). The time between diagnosis of GCA and TCZ onset was shorter in the SC TCZ group. Regarding acute phase reactants at the beginning of TCZ, no differences were found between both groups. There were no significant differences in sustained remission or in glucocorticoid-sparing effect of TCZ (FIGURE). Patients on IV TCZ treatment suffered more relevant adverse effects during follow-up.

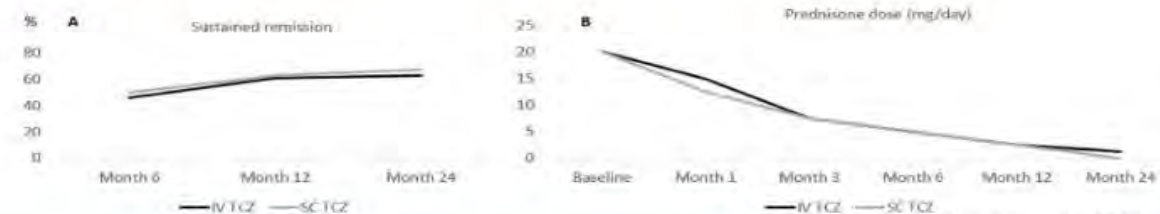
CONCLUSION

In GCA, TCZ seems equally effective and safe regardless of the route of administration IV or SC.

TABLE. Main features of GCA patients treated with intravenous and subcutaneous tocilizumab.

	IV TCZ (n= 238)	SC TCZ (n=233)	P
Baseline characteristics at TCZ onset			
Age(years), mean±SD	73.3±8.7	73.7±9.3	0.63
Sex, female/male (% female)	175/63 (73)	167/66 (72)	0.65
Time from GCA diagnosis to TCZ onset (months), median [IQR]	8 [3-23.5]	5 [2-15]	0.016
ESR, mm 1st hour, median [IQR]	30.5 [12.5-53]	28 [10-56.5]	0.66
CRP, mg/dL, median [IQR]	1.4 [0.5-2.8]	1.4 [0.4-4]	0.92
Prednisone dose, mg/day, median [IQR]	20 [10-40]	20 [10-36.2]	0.69
Safety after TCZ onset			
Follow-up, (months), median [IQR]	27 [16-44]	14 [6-26.7]	<0.001
Relevant adverse events, n (%)	80 (34)	46 (19)	<0.001
Relevant adverse events per 100 patients-year	12.7	15.2	NS
Serious infections, n (%)	44 (18)	21 (9)	0.44
Serious infections per 100 patients-year	6.7	7.2	NS
MACEs, n (%)	1 (0.4)	0 (0)	-
MACEs per 100 patients-year	0.1	0	NS
Malignancies, n (%)	4 (1.7)	1 (0.4)	0.20
Malignancies per 100 patients-year	0.6	0.3	NS

FIGURE. A) Sustained remission, and B) prednisone dose required in GCA patients treated with intravenous and subcutaneous tocilizumab.



INTRAVENOUS VERSUS SUBCUTANEOUS TOCILIZUMAB IN A SERIES OF 471 PATIENTS WITH GIANT CELL ARTERITIS

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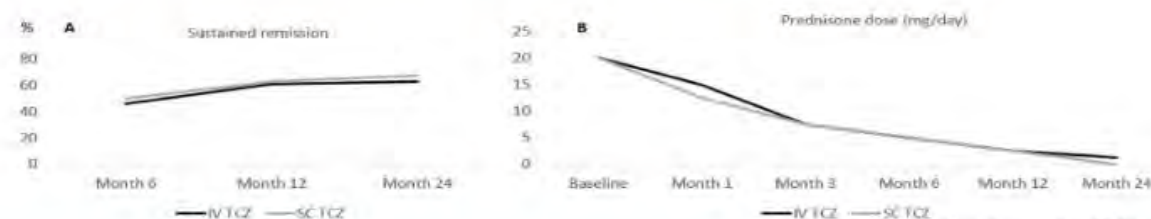
¹Rheumatology, Hospital Universitario Marqués de Valdecilla, Santander, Spain. ²Hospital Universitario de La Princesa, IIS-Princesa, Catedra UAM-Roche, EPID-Future, UAM, Madrid. ³Complejo Asistencial Universitario de León, León. ⁴Hospital de Bellvitge, Barcelona. ⁵Complejo Hospitalario de Navarra, Pamplona. ⁶Hospital Universitario de Donostia, San Sebastián. ⁷Complejo Hospitalario Universitario de Vigo, Vigo. ⁸Hospital Sierrallana, Torrelavega. ⁹Hospital General Universitario de Alicante, Alicante. ¹⁰Complejo Hospitalario Universitario de Pontevedra, Pontevedra. ¹¹Hospital San Cecilio, Granada. ¹²Hospital La Paz, Madrid. ¹³Hospital de Basurto, Bilbao. ¹⁴Hospital Universitario de Elda, Alicante. ¹⁵Hospital Universitario Juan Canalejo, A Coruña. ¹⁶Complejo Hospitalario Universitario de Canarias, Tenerife. ¹⁷Department of Rheumatology, Hospital Parc Taulí, Barcelona. ¹⁸Hospital Universitario 12 de Octubre, Madrid.

- 238 with IV-TCZ and 233 with SC-TCZ
- The time between diagnosis of GCA and TCZ onset was shorter in the SC TCZ group.
- No differences in:
 - sustained remission
 - glucocorticoid-sparing effect of TCZ (Figure 1).
- Patients on IV TCZ treatment suffered more relevant adverse effects during follow-up.

TABLE. Main features of GCA patients treated with intravenous and subcutaneous tocilizumab.

	IV TCZ (n= 238)	SC TCZ (n=233)	P
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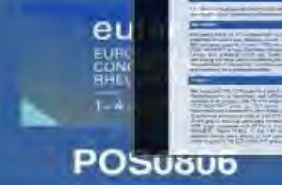
FIGURE. A) Sustained remission, and B) prednisone dose required in GCA patients treated with intravenous and subcutaneous tocilizumab.





OPTIMIZATION OF TOCILIZUMAB THERAPY IN GIANT CELL ARTERITIS. A MULTICENTER REAL-LIFE STUDY OF 471 PATIENTS

Carmen Álvarez-Rieguera; Mónica Calderón-Goercke; Javier Loricera; Clara Morlano; Santos Castañeda; Javier Narváez Vicente Aldasoro; Olga Maiz; Rafael Melero; Juan Ignacio Villa; Paloma Vela; Susana Romero-Yuste; José Luis Callejas; Eugenio de Miguel; Eva Galíndez-Agirregokoa; Francisca Sivera; Jesus Carlos Fernández-López; Carlos Galisteo; Iván Ferraz-Amaro; Julio Sánchez-Martín; Lara Sánchez-Bilbao; José L. Hernández; Miguel Ángel González-Gay; Ricardo Blanco, on behalf of Tocilizumab in Giant Cell Arteritis Spanish Collaborative Group



BACKGROUND

Tocilizumab (TCZ) has shown to be useful in the treatment of large-vessel vasculitis, including giant cell arteritis (GCA) (1-4). There is general agreement on the initial and the standard maintenance dose of TCZ. However, information on duration and optimization of TCZ in GCA is really scarce

OBJECTIVE

Our aim was to assess the effectiveness and safety of TCZ therapy optimization in an unselected wide series of GCA in real-world clinical practice.

METHODS

Multicenter study on 471 patients with GCA who received TCZ therapy. Once complete remission was reached (n=231) TCZ was optimized in 125 patients. We compared patients in whom TCZ was optimized (TCZ OPT group) or not (TCZ NON-OPT group). Complete remission was defined as normalization of clinical and analytical (CRP and ESR) data. Optimization was done by decreasing the dose and/or prolonging the TCZ dosing interval progressively. We performed a comparison in effectiveness and safety parameters between optimized and non-optimized patients.

RESULTS

We evaluated 231 GCA patients treated with TCZ with complete remission. Nodemographic or laboratory data differences was observed at TCZ onset between both groups (TABLE). The mean prednisone dose was higher in the TCZ NON-OPT group at TCZ onset. The first TCZ optimization was performed after a median [25-75th] follow-up of 12 [6-17] months. The median prednisone dose at first TCZ optimization was 2.5 [0-5] mg/day. At the end of follow-up prolonged remission was observed in 78.2% of TCZ OPT group compared with 66.7% in the TCZ NON-OPT group (p= 0.001) (FIGURE). Seven (5.6%) of the 125 optimized cases relapsed. Serious adverse events were similar in both groups, while serious infections were more frequent in the TCZ NON-OPT group (p=0.009).

CONCLUSIONS

Once complete remission is reached in GCA patients under TCZ treatment, optimization of biologic may be performed. Based on our experience it could be performed by reducing the dose or by prolonging dosing interval of TCZ. It seems to be an effective and safe practice.

TABLE 1: MAIN GENERAL FEATURES AT TCZ ONSET OF 231 GCA PATIENTS WITH PROLONGED REMISSION.

	OPTIMIZED – TCZ GROUP (n=125)	NON-OPTIMIZED TCZ GROUP (n=106)	p
GENERAL FEATURES			
Age, years, mean ± SD	72.7±8.6	74±8.7	0.197
Sex, female/male, n (% female)	91/34 (72.8)	74/32 (69.8)	0.616
Time from GCA diagnosis to TCZ onset (months), median [IQR]	8 [2-21.5]	5 [2-21]	0.384
SYSTEMIC MANIFESTATIONS			
Fever, n (%)	14 (11.2)	15 (14.2)	0.500
Constitutional syndrome, n (%)	54 (43.2)	39 (36.8)	0.322
PMR, n (%)	75 (60)	69 (65.1)	0.426
ISCHEMIC MANIFESTATIONS			
Visual involvement, n (%)	14 (11.2)	16 (15.1)	0.380
Headache, n (%)	66 (52.8)	62 (58.5)	0.386
Jaw claudication, n (%)	24 (19.2)	25 (23.6)	0.417
AORTITIS, n (%)	65 (52)	42 (39.6)	0.060
ANALYTICAL FINDINGS			
ESR, mm/1st hour, mean (SD)	39.1±29.3	37.5±33.5	0.334
CRP, mg/dL mean (SD)	2.6± 3.4	2.7± 4	0.305
Hemoglobin, g/dL, mean (SD)	13.5±9.6	12.9±1.5	0.153
GLUCOCORTICOIDS			
Prednisone dose, mg/d mean (SD)	20.3±16.4	27±17.8	0.001

1. Calderón-Goercke M, et al. Semin Arthritis Rheum. 2019; 49: 126-133. PMID: 30655811
 2. Loricera J, et al. Clin Exp Rheumatol. 2016; 34: S44-S53. PMID: 27050507
 3. Prieto-Peña D, et al. Ther Adv Musculoskelet Dis. 2021; 13: 1759720X211026917. PMID: 34211588
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OPTIMIZATION OF TOCILIZUMAB THERAPY IN GIANT CELL ARTERITIS. A MULTICENTER REAL-LIFE STUDY OF 471 PATIENTS

Carmen Álvarez-Figueroa; Mónica Calderón-Goercke; Javier Loricera; Clara Morlano; Santos Castañeda; Javier Narváez Vicente Aldasoro; Olga Maiz; Rafael Melero; Juan Ignacio Villa; Paloma Vela; Susana Romero-Yuste; José Luis Callejas; Eugenio de Miguel; Eva Galíndez-Agirregokoa; Francisca Sivera; Jesus Carlos Fernández-López; Carlos Galisteo; Iván Ferraz-Amaro; Julio Sánchez-Martín; Lara Sánchez-Bilbao; José L. Hernández; Miguel Ángel Gortázar-Gay; Ricardo Blanco, on behalf of Tocilizumab in Giant Cell Arteritis Spanish Collaborative Group



BACKGROUND

- Once complete remission was reached (n=231) TCZ was optimized in 125 patients
- Prolonged remission was observed in 78.2% of optimized group
- 66.7% in the non-opt group (p= 0.001)
- Seven (5.6%) of the 125 optimized cases relapsed.
- Serious adverse events were similar in both groups,
- Serious infections were more frequent in the nonoptimized group (p=0.009).

CONCLUSIONS

Once complete remission is reached in GCA patients under TCZ treatment, optimization of biologic may be performed. Based on our experience it could be performed by reducing the dose or by prolonging dosing interval of TCZ. It seems to be an effective and safe practice.

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Effectiveness of every-other-week tocilizumab maintenance therapy in giant cell arteritis: a prospective single-centre study

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Background. The GiACTA open-label extension phase showed that 58% of patients with giant cell arteritis (GCA) treated with a 12-month course of weekly tocilizumab (TCZ) had a disease flare in the 2 years following therapy suspension¹, thus suggesting that some patients may need a more prolonged treatment.

Objective. To evaluate the efficacy and safety of low-dose TCZ maintenance in GCA patients who achieved remission after one year of standard therapy.

Methods. GCA patients who achieved remission after one year of weekly subcutaneous TCZ were prospectively enrolled. TCZ was administered every-other-week (EOW) for additional 12 months, and eventually suspended.

(Study design illustrated in the **Figure below**)

Primary outcome:

- relapse-free disease maintenance 6 months after tocilizumab suspension

Secondary outcomes:

- relapse-free disease maintenance during tocilizumab therapy
- incidence of adverse events

Results (I).

17 patients were enrolled (12 women, 71%; mean age 71.5 ± 8.7 years).

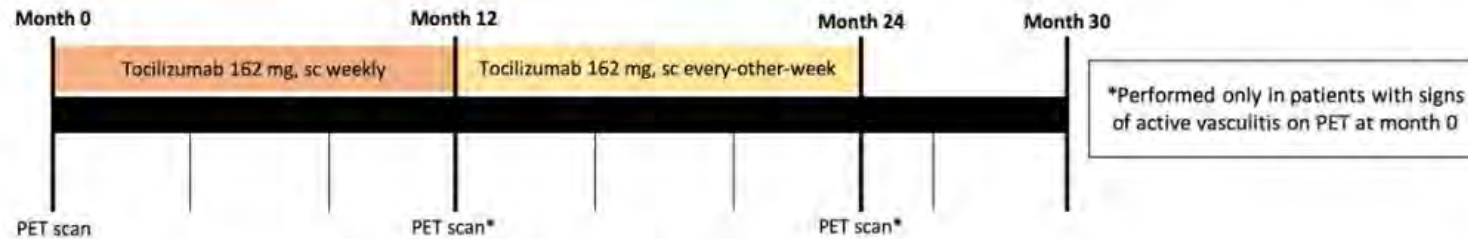
Disease features at diagnosis and TCZ start are listed in the **Table**.

Reasons for TCZ start were clinical or imaging disease flare (n = 9), persistence of disease activity (n = 5), and steroid-related adverse events (n = 3). At TCZ start, median disease duration was 8 (IQR, 3 - 22) months, serum C-reactive protein was 13 (IQR, 6 - 22) mg/L, daily prednisone (PDN) dose was 25 (IQR, 15 - 37.5) mg. Four patients were already on methotrexate (MTX) which was maintained in 1 of them. Ten patients had LV involvement on PET scan.

At TCZ EOW start, no patient was on PDN and 1 patient was on MTX; MTX was added in another patient at month 12 due to persistence of LV involvement on PET scan. All patients completed the 24-month TCZ course. Two patients (12%) had a polymyalgic flare while on EOW TCZ: one patient at month 1 and one patient at month 6; of note, one of them had a polymyalgic flare also while on weekly TCZ. Both flares were managed with a PDN course with complete clinical remission. No patient had active LV involvement at 24-month PET scan. Adverse events on EOW TCZ were zoster reactivation (n = 1) and neutropenia (n = 1).

	Diagnosis, n=17 n (%)	TCZ start, n=17 n (%)
Headache	16 (94)	5 (29)
Scalp tenderness	11 (65)	5 (29)
Jaw claudication	9 (53)	2 (12)
Ocular manifestations	3 (17)	0 (0)
Polymyalgia rheumatica	8 (47)	0 (0)
Constitutional symptoms	14 (82)	7 (47)
Active vasculitis on PET	10 (59)	10 (59)
CRP levels (mg/L), mean ± SD	70 ± 36	16 ± 13
Modality of diagnosis		
Vascular ultrasound	7 (47)	-
Temporal artery biopsy	3 (17)	-
PET	10 (59)	10 (59)

Clinical features of GCA patients at diagnosis and at tocilizumab start



Steroid therapy tapered according to the 26-week scheme used in the GiACTA trial
Relapse = recurrence of signs or symptoms attributable to GCA, which resolved after therapy increase

Results (II).

At TCZ stop, no patient was on PDN and 2 patients were on MTX. One month after TCZ stop, all patients were in remission. Six months after TCZ stop, 4 patients (24%) experienced a flare with mixed features, which was successfully managed in all cases with TCZ weekly re-introduction; in 2 patients, a PDN course was also started.

Conclusions.

In this proof-of-concept study, low-dose TCZ maintenance in GCA showed excellent disease control, which was maintained in most (*but not all*) patients after therapy suspension.

Therefore, should low-dose tocilizumab be maintained indefinitely in selected patients?

Longer follow-up and replication in larger cohorts are required.

Effectiveness of every-other-week tocilizumab maintenance therapy in giant cell arteritis: a prospective single-centre study

Alessandro Tomelleri*, Corrado Campochiaro, Letizia Mariotti, Silvia Sartorelli, Nicola Farina, Elena Baldissera, Lorenzo Dagna
Unit of Immunology Rheumatology Allergy and Rare Diseases, IRCCS San Raffaele Hospital, Milan, Italy



- After remission was achieved 17 patients continued TOCI every other week for an additional 12 months
- Low-dose TCZ maintenance in GCA showed excellent disease control
- Two patients (12%) had a polymyalgic flare while on EOW
- No patient had active LV involvement at 24-month PET scan.
- Adverse events on EOW TCZ were zoster reactivation (n=1) and neutropenia (n=1).

	Diagnosis, n=17 n (%)	TCZ start, n=17 n (%)
Headache	16 (94)	5 (29)
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Clinical features of GCA patients at diagnosis and at tocilizumab start

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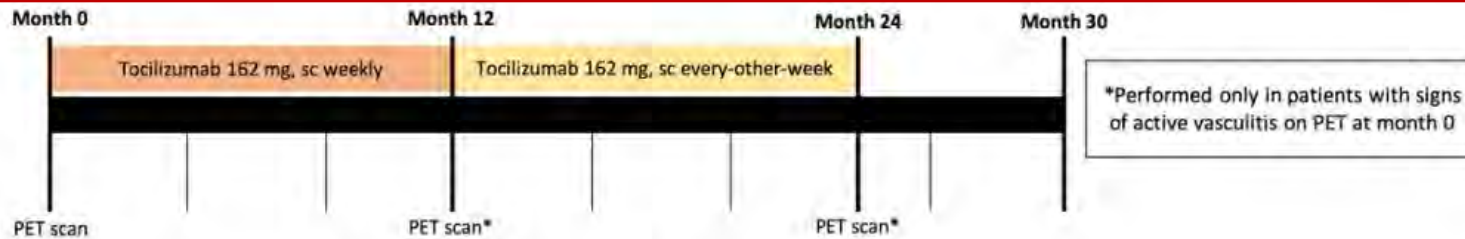
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Steroid therapy tapered according to the 26-week scheme used in the GiACTA trial
Relapse = recurrence of signs or symptoms attributable to GCA, which resolved after therapy increase

Glucocorticoids, conventional DMARDs and tocilizumab differently affect ¹⁸F-FDG PET metabolic activity in giant cell arteritis patients.

Luca Iorio¹, Debora Campaniello¹, Pietro Zucchetto², Diego Cecchin², Andrea Doria¹, Franco Schiavon¹, Roberto Padoan¹

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EULAR PN: POSo813

BACKGROUND: Imaging role in large vessel vasculitis (LVV) patients is tremendously increased in recent years. However, the role of ¹⁸F-FDG PET in evaluating treatment response is still an unmet need.

OBJECTIVES: The aim of the present study is to evaluate the effect of different treatment regimens, namely glucocorticoids (GC), conventional disease modifying anti-rheumatic drugs (cDMARDs) and tocilizumab (TCZ), on clinical and metabolic activity of giant cell arteritis (GCA) with extracranial involvement.

METHODS: Consecutive LVV inpatients and outpatients, classified as GCA, were prospectively enrolled. We included all patients who underwent to at least 2 consecutive ¹⁸F-FDG PET-CT or MR scan between October 2010 and October 2021. Demographic and clinical data as well as disease activity were assessed before every PET scan. Remission was defined absence of signs and symptoms attributable to GCA and normalization of ESR (<30 mm/Hr) and CRP (<1 mg/dL) [1]. GCA patients were compared according to current treatment regimen: GC monotherapy versus cDMARDs (methotrexate, azathiopirine) and versus TCZ (administered both subcutaneous and intravenous). For each PET scan the vessel's metabolic activity was evaluated using the Meller's grading [2] and the PETVAS score [3].

RESULTS: The study included 47 patients (age 66 [60-70], 72.3% female) exposed to a total of 77 treatment regimens (n=37 GC monotherapy, n=26 cDMARDs, n=14 TCZ). A total of 181 PET scan were conducted (min 2 – max 6). Overall clinical remission rate during the follow-up was 75.7% in GC-treated patients, 69.2% in cDMARDs-treated and 85.7% in TCZ-treated (p=0.513). Persistence was comparable among the different treatment regimens (GC 19±10 months vs cDMARDs 22±16 months vs TCZ 23±11 months, p=0.445). All the treatment led to significant reduction of acute phase reactants (GC-treated: ESR 50vs20 mmh, p<0.001, ΔESR= -43.3%, CRP 13.6vs5.3 mg/L, p=0.001, ΔCRP= -87.7%; cDMARDs treated: ESR 36vs27 mmh, p=0.134, ΔESR= -152%, CRP 13.6vs5.3 mg/L, p=0.038, ΔCRP= -66.3% and TCZ-treated: ESR 27vs3 mmh, p=0.017, ΔESR= -86.7%, CRP 11.4vs2.7 mg/L, p=0.023, ΔCRP= -80.2%).

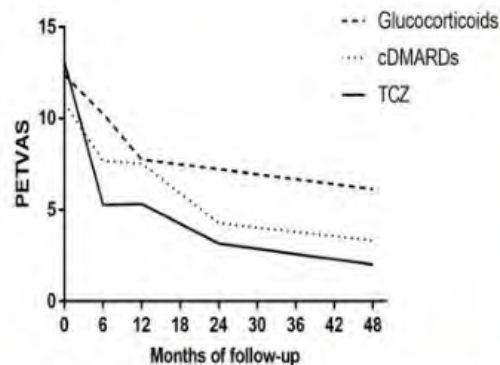


Figure. The PETVAS score reduction according to different treatment regimens.

Significant improvement in PETVAS was observed only in TCZ-treated patients (12vs4, p=0.002, ΔPETVAS -66.7%), while the other treatment approaches resulted not significant (GC treated 12vs5, p=0.052, ΔPETVAS= -50%; cDMARDs 11vs4, p=0.124, ΔPETVAS -52.4%). Daily prednisone dose at last examination was 4.5 [0-5] mg/d in the cDMARDs group vs 1.25 [0-5] mg/d in the TCZ group (p=0.057). Interestingly, at last PET examination low-grade inflammation (Meller 1-2) was observed in 56.8% of GC-treated patients, 57.7% of cDMARDs treated patients and 64.3% of TCZ-treated patients (p=0.884).

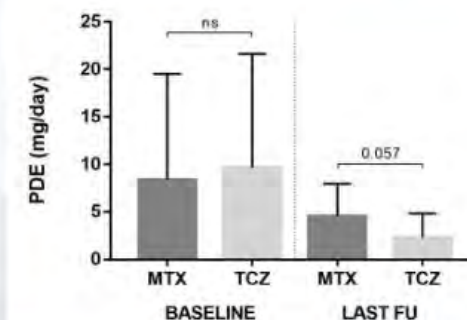


Figure. PDE (prednisolone dose equivalent) in MTX-treated patients vs TCZ-treated patients at baseline and last follow up

Table 1. Baseline and last follow-up data of 77 treatment regimens

	ESR				CRP				PETVAS			
	Baseline	LFU	p value	ΔESR	Baseline	LFU	p value	ΔCRP	Baseline	LFU	p value	ΔPETVAS
GC (n=37)	50	20	<0.001	-43.3%	13.6	5.3	0.001	-87.7%	12	5	0.052	-50%
cDMARDs (n=26)	36	27	0.134	-152%	13.6	5.3	0.038	-66.3%	11	4	0.124	-52.4%
TCZ (n=14)	27	3	0.017	-86.7%	11.4	2.7	0.023	-80.2%	12	4	0.002	-66.7%

ESR (erythrocyte sedimentation rate), CRP (c-reactive protein), PETVAS (PET vascular activity score), LFU (last follow up)



Figure. Comparison between highly pathological FDG-PET uptake (Meller 3) at baseline and low-grade uptake (Meller 1) at last follow up.

CONCLUSIONS:

- ¹⁸F-FDG PET may be useful in assessing disease activity and monitoring response to therapy.
- Tocilizumab treatment significantly reduce vessel's metabolic activity over time, when compared to conventional treatment.
- A persistent low-grade uptake during remission is common features in LVV patients, irrespectively of treatment regimens.

Glucocorticoids, conventional DMARDs and tocilizumab differently affect ¹⁸F-FDG PET metabolic activity in giant cell arteritis patients.

Luca Iorio¹, Debora Campaniello¹, Pietro Zucchetta², Diego Cecchin², Andrea Doria¹, Franco Schiavon¹, Roberto Padoan¹
¹University of Padua, Division of Rheumatology, Department of Medicine DIMED, Padova, Italy,
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EULAR PN: POSo813

- 47 patients who had at least 2 PETCT or PETMRI scan
- Clinical remission rate: 76% in GC, 69% in cDMARD, and 86% in TCZ- (p=0.513).
- Significant improvement in PETVAS was observed only in TCZ-treated patients ,
- Interestingly, at last PET examination low-grade inflammation was observed in 57% of GC-treated patients, 58% of cDMARDs-treated patients and 64% of TCZ-treated patients (p=0.884).
- ¹⁸F-FDG PET may be useful in assessing disease activity and monitoring response
- Tocilizumab treatment significantly reduce vessel's metabolic activity over time

RESULTS: The study included 47 patients (age 66 [60-70], 79.2% female) exposed to a total of 77 treatment regimens (n=37 GC monotherapy, n=26 GC + DMARDs, n=2 - max 6). Overall clinical remission rate during the follow-up was 76% in GC, 69% in cDMARDs and 86% in TCZ-treated (p=0.513). Persistence was comparable among the different treatment regimens (11 months, p=0.445). All the treatment led to significant reduction of acute phase reactants: CRP 13.6vs5.3 mg/L, p=0.001, ΔCRP= -87.7%; cDMARDs treated: ESR 36vs27 mmh, p=0.001, ΔESR= -25.0% and TCZ-treated: ESR 27vs3 mmh, p=0.017, ΔESR= -86.7%, CRP 11.4vs2.7 mg/L, p=0.001, ΔCRP= -76.3%.

Improvement in PETVAS was observed only in TCZ-treated patients (12vs4, p=0.002), while the other treatment regimens did not show a significant improvement (GC treated 12vs5, p=0.002, ΔS= -50%; cDMARDs 11vs4, p=0.002, ΔS= -52.4%). Daily prednisone dose at last PET examination was 4.5 [0-5] mg/d in the cDMARDs treated patients (p=0.057). At last PET examination low-grade inflammation (Meller 1-2) was observed in 56.8% of GC-treated patients, 57.7% of cDMARDs treated patients and 64% of TCZ-treated patients.

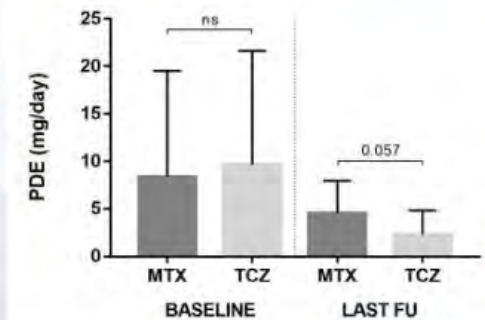


Figure. PDE (prednisolone dose equivalent) in MTX-treated patients vs TCZ-treated patients at baseline and last follow up



Low-grade ¹⁸F-FDG-PET uptake (Meller 1) at last follow up.

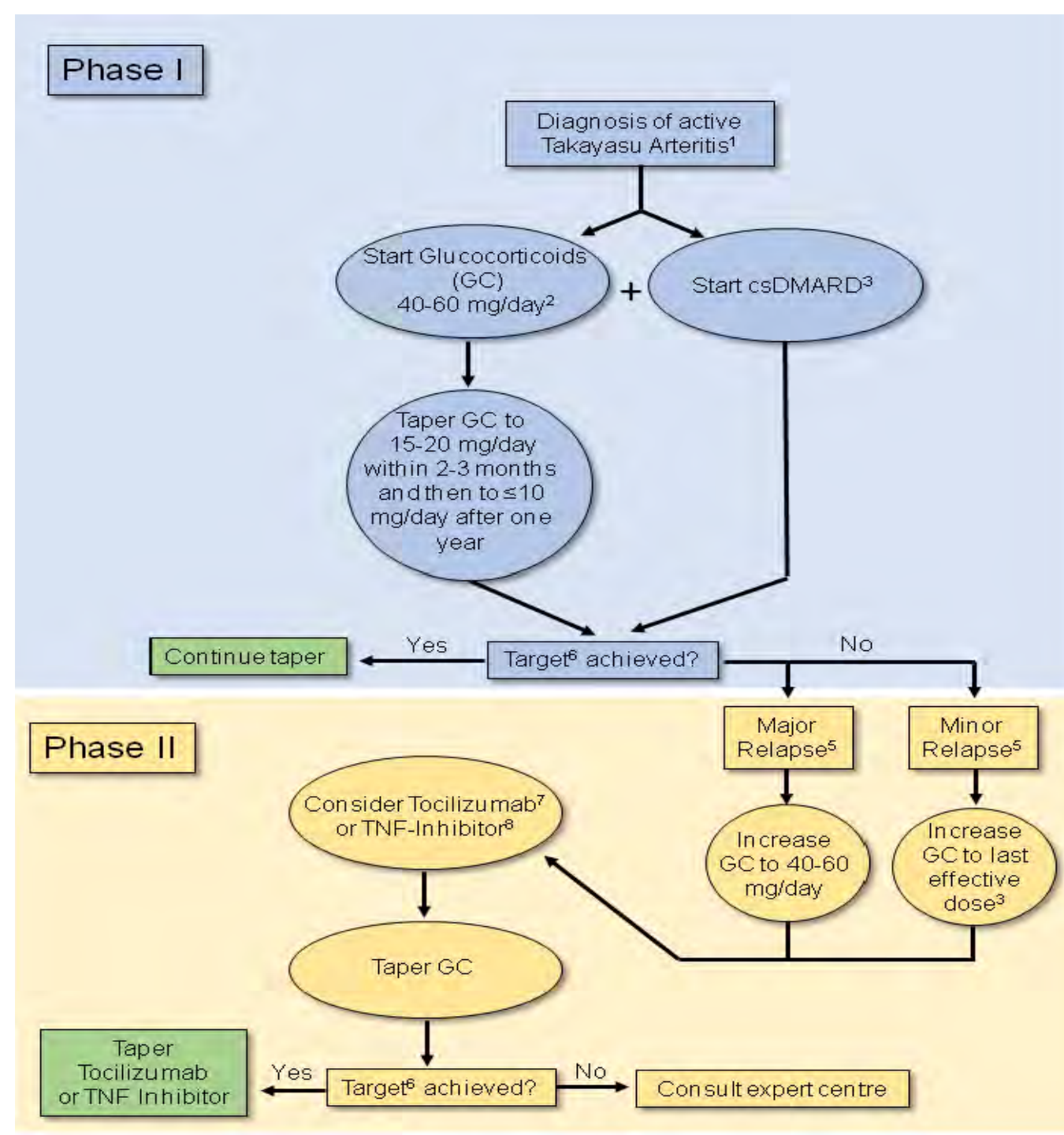
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- A persistent low-grade uptake during remission is common features in LVV patients, irrespectively of treatment regimens.

2018 Update of the EULAR recommendations for the management of large vessel vasculitis

Bernhard Hellmich¹, Ana Agueda², Sara Monti³, Frank Buttgereit⁴, Hubert de Booysson⁵, Elisabeth Brouwer⁶, Rebecca Cassie⁷, Maria C Cid⁸, Bhaskar Dasgupta⁹, Christian Dejaco^{10,11}, Gulen Hatemi¹², Nicole Hollinger¹³, Alfred Mahr¹⁴, Susan P Mollan^{15,16}, Chetan Mukhtyar¹⁷, Cristina Ponte^{18,19}, Carlo Salvarani²⁰, Rajappa Sivakumar²¹, Xiping Tian²², Gunnar Tomasson²³, Carl Turesson²⁴, Wolfgang Schmidt²⁵, Peter M Villiger²⁶, Richard Watts²⁷, Chris Young²⁸, Raashid Ahmed Luqmani²⁹

Management of Takayasu Arteritis



Efficacy and safety of tofacitinib versus leflunomide treatment in Takayasu arteritis: a prospective study

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BACKGROUND/OBJECTIVES

Takayasu arteritis (TAK) is a rare large-vessel vasculitis characterized by vascular granulomatous inflammation. Those involved arteries can progress into stenosis, occlusion. Thus, effective treatment is in need to improve patients' prognosis.

To date, glucocorticoids (GCs) and immunosuppressants remain as the first-line therapy for TAK patients. LEF, functions as an inhibitor of pyrimidine synthesis, has been widely used in a variety of autoimmune disease. In terms of its mechanism, it probably also participated in the improvement of vascular fibrosis in TAK via down-regulating M2 macrophage polarization [1]. Thus, LEF has now been well-accepted in TAK treatment.

Tofacitinib (TOF) is a JAK1/JAK3 signaling pathway inhibitor. In TAK, increasing evidence has suggested that JAK/STAT signaling pathway played an essential role in the pathogenesis of TAK [2, 3]. According to our recent study, TOF is superior to MTX for complete remission (CR) induction, relapse prevention and tapering of the GCs dose [4]. However, its efficacy needs further confirmation.

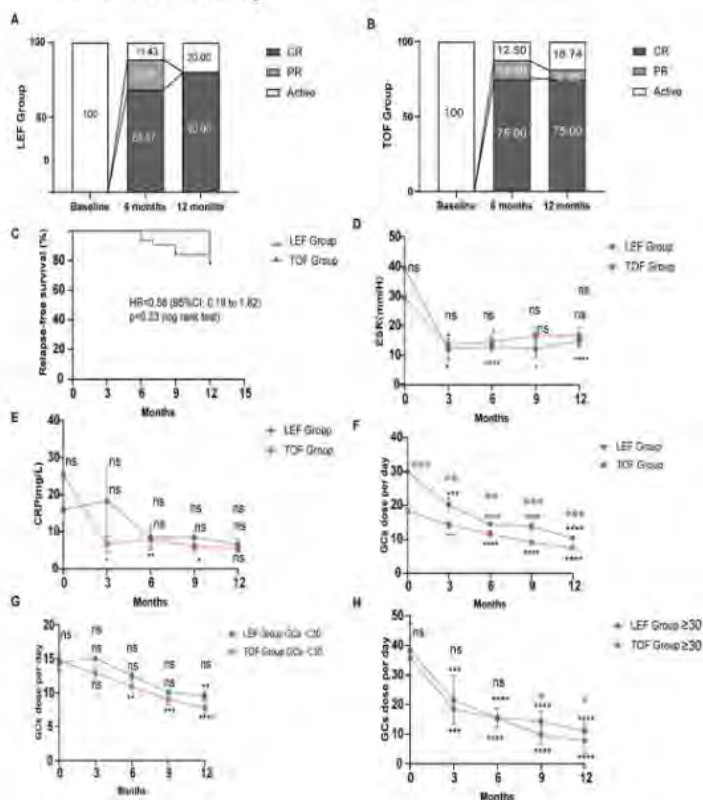
Thus, this study aimed to compare the effectiveness and safety of TOF with another effective agent, LEF in patients with TAK.

METHODS

- Respondents: A total of 67 patients with active disease screened from the prospective East China Takayasu Arteritis (ECTA) cohort were recruited in this study. Among them, 35 patients were treated with glucocorticoids (GCs) and LEF and 32 patients were treated with GCs and TOF.
- * Methods: Patients were followed up according to a pre-designed plan and assessed by a professional team with rheumatologist, radiologist and vascular surgeon.

RESULTS

* Treatment efficacy.



CONCLUSIONS

- This study firstly demonstrated a comparable effectiveness between TOF and LEF in TAK treatment.
- LEF or TOF are effective in inducing and maintaining remission, inflammatory index reduction, and GCs tapering.
- TOF is superior to LEF in terms of GCs reduction and safety.

* Limits: small sample size, short observation time, and samples selection bias.

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Efficacy and safety of tofacitinib versus leflunomide treatment in Takayasu arteritis: a prospective study

Jinghua Wang1#, Xiaojuan Dai1#, Ying Sun1, Sifan Wu1, Li Wang1, Wensu Yu1, Zongfei Ji1, Lingying Ma1, Xiaomin Dai1, Zhuojun Zhang1, Yun Liu1, Rongyi Chen1, Huiyong Chen1, Lili Ma1, Lindi Jiang1,2*, Xiufang Kong1*

1 Department of Rheumatology, Zhongshan Hospital affiliated to Fudan University, Shanghai, China.

2 Center of Clinical Epidemiology and Evidence-based Medicine, Fudan University, Shanghai, China.



- 67 active TAK
 - 35 LEF
 - 32 TOFA
- LEF and TOF have comparable treatment effects for patients with TAK.
 - 31/35 (88.57%) vs. TOF group: 28/32 (87.50%), $p=1.00$).
- Relapse rate was also comparable between two groups
 - (LEF group: 6 (17.14%) vs. TOF group 7 (21.88%), $p=0.76$).
- However, TOFA is superior to LEF in GCs tapering and safety profile
 - (12/35, 34.29%, vs 3/32, 9.38%; $p=0.02$).

Thank you