VASCULITIS SISTEMICAS

THE “TOP 5”

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Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis

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METHODS

We compared rituximab with cyclophosphamide as induction therapy in ANCA-associated vasculitis. We randomly assigned, in a 3:1 ratio, 44 patients with newly diagnosed ANCA-associated vasculitis and renal involvement to a standard glucocorticoid regimen plus either rituximab at a dose of 375 mg per square meter of body-surface area per week for 4 weeks, with two intravenous cyclophosphamide pulses (33 patients, the rituximab group), or intravenous cyclophosphamide for 3 to 6 months followed by azathioprine (11 patients, the control group). Primary end points were sustained remission rates at 12 months and severe adverse events.

RITUXIVAS

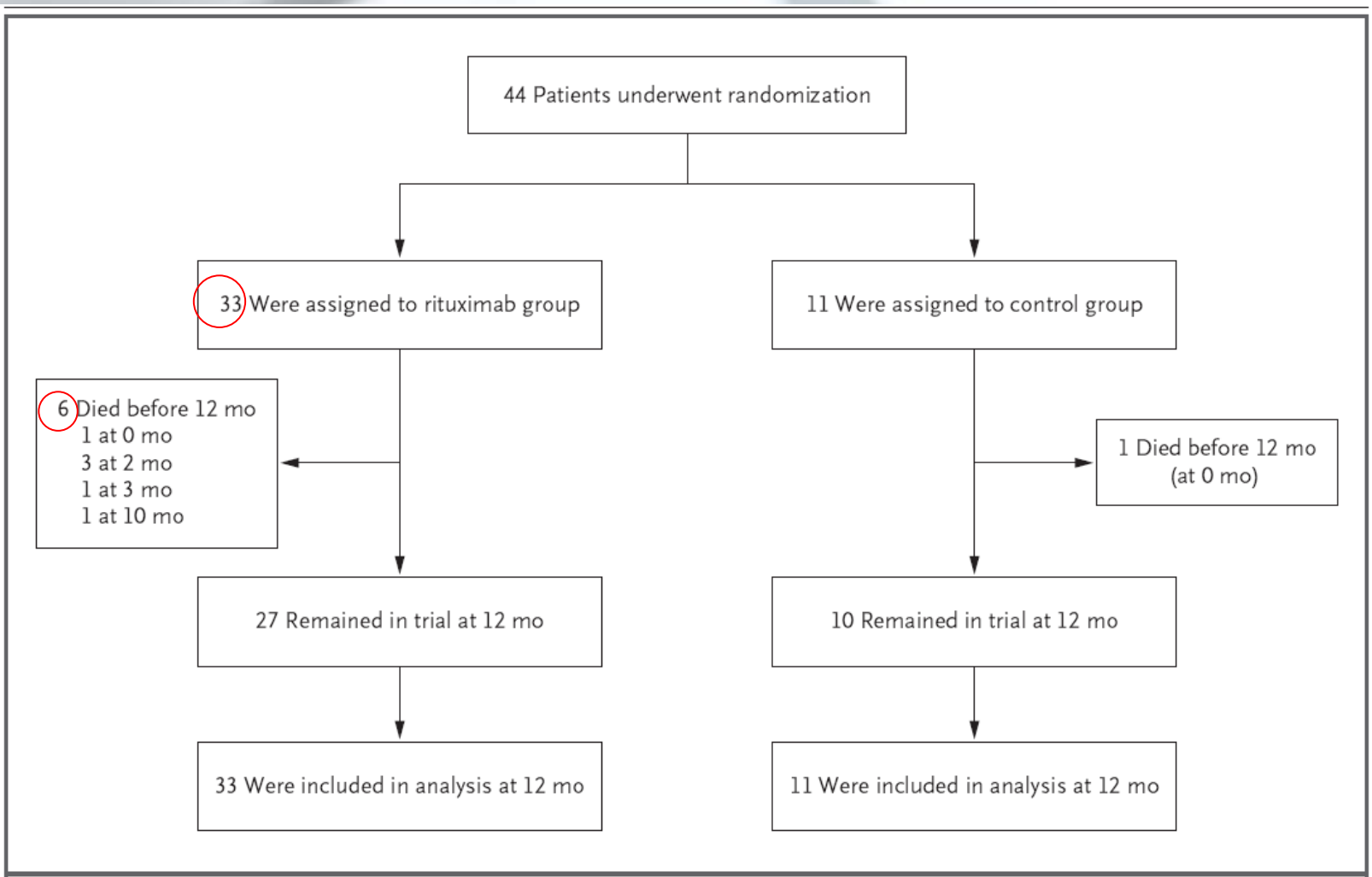


Figure 1. Randomization and Inclusion in the Analysis at 12 Months.

In the control group, a second patient died at 20 months.

Table 1. Demographic and Clinical Characteristics of the Patients at Trial Entry.*

Variable	Rituximab Group (N=33)	Control Group (N=11)
Age — yr		
Median	68	67
Interquartile range	56–75	58–76
Male sex — no. (%)	17 (52)	6 (55)
Diagnosis — no. (%)		
Wegener's granulomatosis	18 (55)	4 (36)
Microscopic polyangiitis	12 (36)	4 (36)
Renal-limited vasculitis	3 (9)	3 (27)
Proteinase 3 and myeloperoxidase–ANCA binding — U/ml		
Median	53	79
Interquartile range	14–100	28–163
ANCA-positive labeling pattern — no. (%)		
Cytoplasmic	20 (61)	5 (45)
Perinuclear	13 (39)	6 (55)
Glomerular filtration rate — ml/min/1.73 m^2†		
Median	20	12
Interquartile range	5–44	9–33
Organs involved — no.		
Median	3	2
Interquartile range	1–4	1–4
Birmingham Vasculitis Activity Score		
Median	19	18
Interquartile range	14–24	12–25
C-reactive protein — mg/dl		
Median	28	25
Interquartile range	12–87	7–87
Erythrocyte sedimentation rate — mm/hr		
Median	52	64
Interquartile range	14–82	21–106
Dialysis required at entry — no. (%)	8 (24)	1 (9)
Intravenous methylprednisolone — g		
Median	1	1
Interquartile range	1–1	1–1
Use of plasma exchange — no. (%)	8 (24)	3 (27)

• 25/33 pacientes (76%) en el grupo de RTX y 9/11 pacientes (82%) en el grupo control lograron el *end point*: remisión mantenida a los 12 meses (2 pacientes en el grupo de RTX recibieron una 3ª dosis de CF). Solo 2 de los 27 pacientes del grupo RTX que sobrevivieron no alcanzaron la remisión mantenida

• El 96% de los pacientes del grupo RTX y el 89% de los del grupo control solo recibían 5 mg prednisona al día a los 9 meses

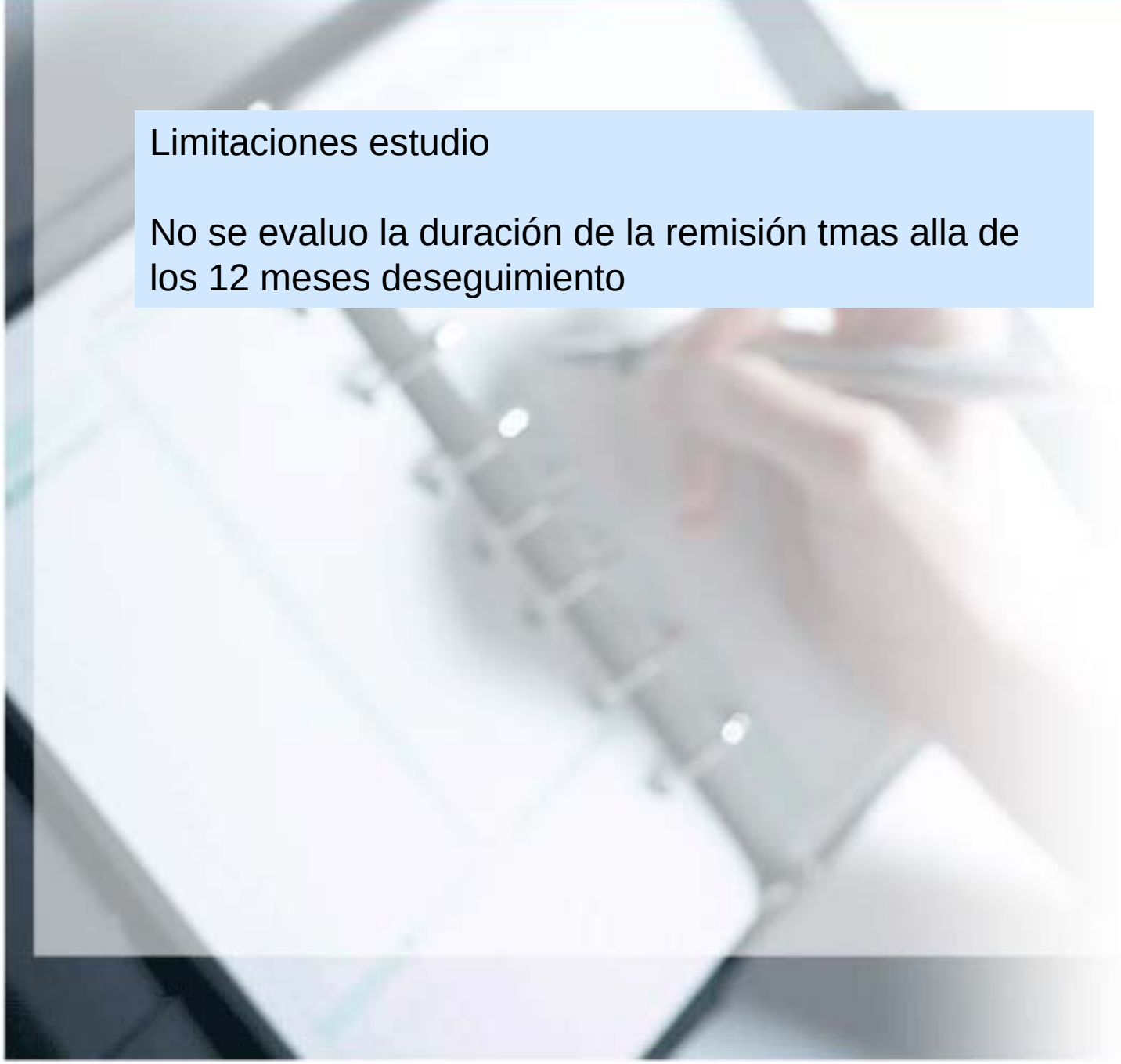
• 6 de los 8 pacientes del grupo RTX que precisaron diálisis a la entrada en el estudio, alcanzaron remisión mantenida y 5 no precisaron continuar dializándose

• 14/33 pacientes (42%) en el grupo de RTX y 4/11 (36%) en el grupo control, presentaron efectos adversos graves.

• 6 pacientes (18%) de grupo de RTX y 2 de grupo control (18%) fallecieron en los 12 primeros meses (tiempo medio hasta la muerte 81 días, edad media al fallecer 76 años, FG inicial 9 ml/min))

Table 2. Adverse Events.*

Events	Rituximab Group (N=33)		Control Group (N=11)	
	All Events	Patients with ≥1 Event	All Events	Patients with ≥1 Event
	no.	*no. (%)*	*no.*	*no. (%)*
Grade 1–5 events†				
Grade 1 or 2	37	21 (64)	14	6 (55)
Grade 3, 4, or 5	31	14 (42)	12	4 (36)
All	68	25 (76)	26	7 (64)
Serious events				
Events requiring hospitalization or life-threatening events	27	12 (36)	9	4 (36)
Cancer	2	2 (6)‡	0	0
Death	6	6 (18)	2	2 (18)
All	35	16 (48)	11	4 (36)
Types of events				
Serious infections	7	6 (18)	3	2 (18)
All infections	19	12 (36)	7	3 (27)
All infusion reactions	2	2 (6)	0	0
Hematologic events				
Anemia	2	2 (6)	2	2 (18)
Neutropenia	2	2 (6)	1	1 (9)
Thrombocytopenia	1	1 (3)	0	0
Hypogammaglobulinemia	1	1 (3)	0	0



Limitaciones estudio

No se evaluo la duración de la remisión tmas alla de los 12 meses deseguimiento

CONCLUSIONS

A rituximab-based regimen was not superior to standard intravenous cyclophosphamide for severe ANCA-associated vasculitis. Sustained-remission rates were high in both groups, and the rituximab-based regimen was not associated with reductions in early severe adverse events. (Funded by Cambridge University Hospitals National Health Service Foundation Trust and F. Hoffmann–La Roche; Current Controlled Trials number, ISRCTN28528813.)

Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis

John H. Stone, M.D., M.P.H., Peter A. Merkel, M.D., M.P.H., Robert Spiera, M.D., Philip Seo, M.D., M.H.S., Carol A. Langford, M.D., M.H.S., Gary S. Hoffman, M.D., Cees G.M. Kallenberg, M.D., Ph.D., E. William St. Clair, M.D., Anthony Turkiewicz, M.D., Nadia K. Tchao, M.D., Lisa Webber, R.N., Linna Ding, M.D., Ph.D., Lourdes P. Sejismundo, R.N., B.S.N., Kathleen Mieras, C.C.R.P., David Weitzenkamp, Ph.D., David Ikle, Ph.D., Vicki Seyfert-Margolis, Ph.D., Mark Mueller, B.S., C.C.R.P., Paul Brunetta, M.D., Nancy B. Allen, M.D., Fernando C. Fervenza, M.D., Ph.D., Duvuru Geetha, M.D., Karina A. Keogh, M.D., Eugene Y. Kissin, M.D., Paul A. Monach, M.D., Ph.D., Tobias Peikert, M.D., Coen Stegeman, M.D., Ph.D., Steven R. Ytterberg, M.D., and Ulrich Specks, M.D., for the RAVE–ITN Research Group*

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METHODS

We conducted a multicenter, randomized, double-blind, double-dummy, noninferiority trial of rituximab (375 mg per square meter of body-surface area per week for 4 weeks) as compared with cyclophosphamide (2 mg per kilogram of body weight per day) for remission induction. Glucocorticoids were tapered off; the primary end point was remission of disease without the use of prednisone at 6 months.

RAVE

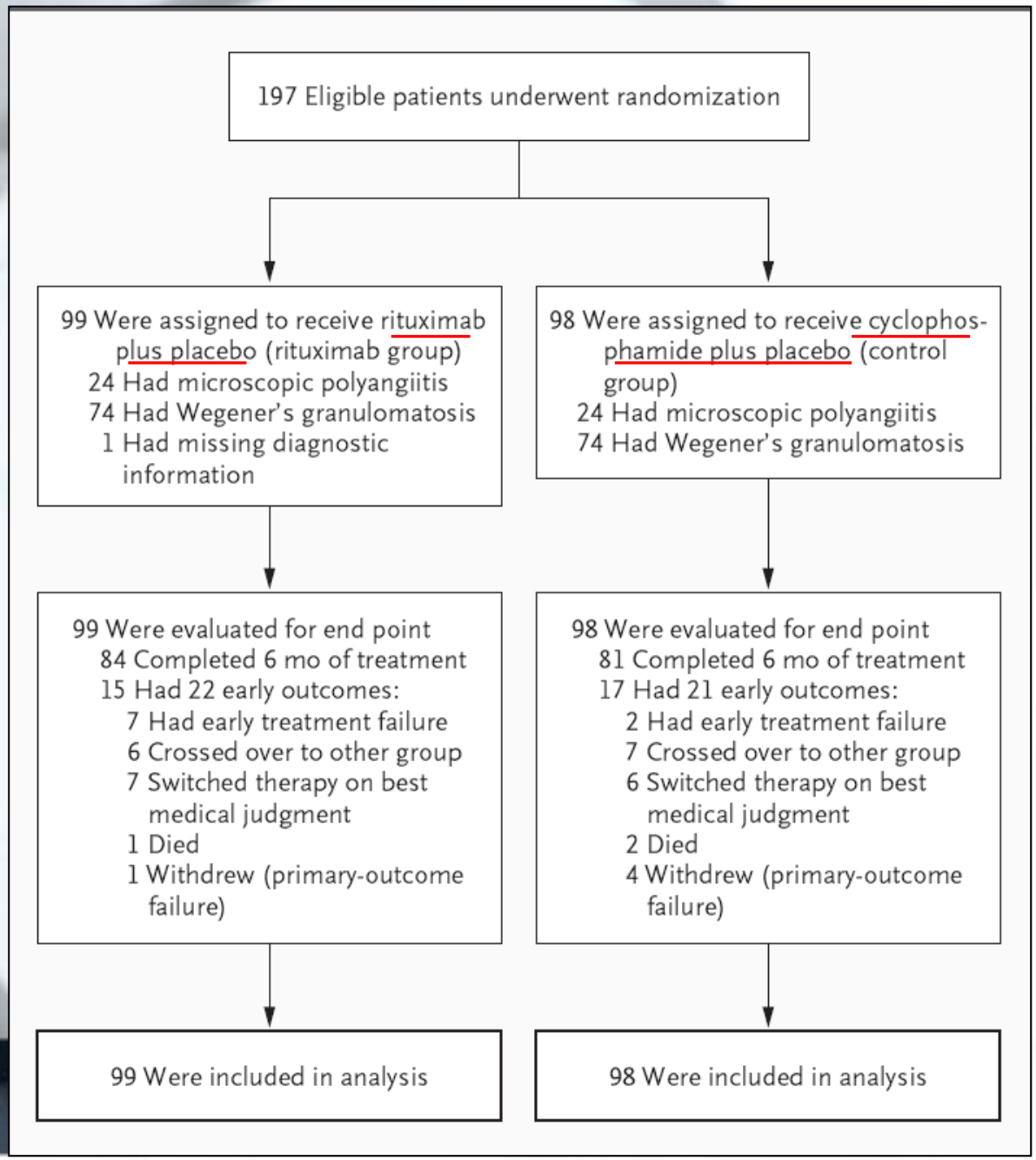
197 Eligible patients underwent randomization
99 Were assigned to receive rituximab plus placebo (rituximab group)
24 Had microscopic polyangiitis
74 Had Wegener's granulomatosis
1 Had missing diagnostic information
98 Were assigned to receive cyclophosphamide plus placebo (control group)
24 Had microscopic polyangiitis
74 Had Wegener's granulomatosis
99 Were evaluated for end point
84 Completed 6 mo of treatment
15 Had 22 early outcomes:
7 Had early treatment failure
6 Crossed over to other group
7 Switched therapy on best medical judgment
1 Died
1 Withdrew (primary-outcome failure)
98 Were evaluated for end point
81 Completed 6 mo of treatment
17 Had 21 early outcomes:
2 Had early treatment failure
7 Crossed over to other group
6 Switched therapy on best medical judgment
2 Died
4 Withdrew (primary-outcome failure)
99 Were included in analysis
98 Were included in analysis

Table 1. Baseline Demographic and Clinical Characteristics of the Patients.*

Variable	Rituximab Group (N=99)	Control Group (N=98)	P Value
Age at onset of symptoms (yr)	54.0±16.8	51.5±14.1	0.26
Sex (%)			0.29
Male	46	54	
Female	54	46	
ANCA-associated vasculitis type (%)			0.61
Wegener's granulomatosis†	75	76	
Microscopic polyangiitis	24	24	
Indeterminate	1	0	
Newly diagnosed at enrollment (%)	48	49	0.62
Pre-enrollment disease duration in patients with relapsed	6.5±6.7	5.3±7.4	0.31
Pre-enro			.10
Disease			
BVA			.38
Phys			.67
Vasc			.17
SF-3			
			.38
			.20
Organ i			
Cons			.12
Cutaneous involvement (%)	20	16	0.48
Mucous membranes and eyes (%)	27	26	0.78
Ear, nose, and throat (%)	61	56	0.52
Pericarditis (%)	0	1	0.50
Mesenteric ischemia (%)	2	0	0.50
Pulmonary involvement (%)	52	54	0.83
Alveolar hemorrhage	27	24	0.54
Endobronchial lesions	4	9	0.15
Nodules or cavities	18	28	0.12
Other lung infiltrate	25	21	0.53
Pleurisy	8	9	0.78
Respiratory failure	2	0	0.50

Se excluyeron pacientes con insuficiencia renal grave (creat > 4 mg/dl) y/o hemorragia pulmonar grave (ventilación mecánica)

No se incluyeron pacientes ANCA negativos (formas limitadas WG)

- 63 pacientes (64%) tratados con RTX alcanzaron el objetivo primario (remisión sin uso de prednisona a los 6 meses) vs 52 (53%) en el grupo control.
- RTX fue mas eficaz que la CF para alcanzar la remisión en pacientes con enfermedad recidivante (34/51 67% vs 21/50 42%).
- RTX fue igual de eficaz que la CF induciendo la remisión en pacientes con enfermedad renal moderada (creat < 4 mg/dl) o hemorragia alveolar no grave.
- 50% pacientes C-ANCA + en grupo RTX y 17% pacientes en grupo control: ANCA negativos a los 6 meses y 40% vs 41% de los pacientes P-ANCA +.

Table 2. Adverse Events at 6 Months.*

Variable	Rituximab Group (N=99)	Control Group (N=98)	Total (N=197)
Total no. of selected adverse events†	31	33	64
>1 Selected adverse event — no. of patients (%)	22 (22)	32 (33)	54 (27)
Annual rate of selected adverse events — %	5	6	6
Specific selected adverse events — no. of events (%)†			
Death	1 (1)	2 (2)	3 (2)
Cancer	1 (1)	1 (1)	2 (1)
Leukopenia (≥grade 2)	3 (3)	10 (10)	13 (7)
Thrombocytopen			4 (2)
Infection (≥grade			14 (7)
Hemorrhagic cystitis	1 (1)	1 (1)	2 (1)
Venous thrombotic event	6 (6)	9 (9)	15 (8)
Cerebrovascular accident	0	0	0
Hospitalization due to disease or treatment	8 (8)	2 (2)	10 (5)
Infusion reaction preventing further infusions of investigational medication	1 (1)	0	1 (<1)
All adverse events — no.	1035	1016	2051
All adverse events ≥grade 3 and serious adverse events — no.	79	78	157
All non–disease-related adverse events ≥grade 3 and serious adverse events — no.	58	53	111
Patients with ≥1 non–disease-related adverse event — %	29	29	58
All adverse events ≥grade 3 and serious adverse events leading to treatment discontinuation — no.	6	8	14
Grade 3 adverse events — no.	61	77	138
≥1 Grade 3 adverse event — no. of patients (%)	22 (22)	32 (33)	54 (27)
Grade 4 adverse events — no.	11	5	16
≥1 Grade 4 adverse event — no. of patients (%)	8 (8)	4 (4)	12 (6)
Grade 5 adverse events (death) — no.	1 (1)	2 (2)	3 (2)

No diferencias significativas, pero el periodo de seguimiento fue muy corto

Limitaciones estudio

- No se incluyeron formas graves
- No se incluyeron formas limitadas ANCA negativas (WG)
- El periodo de seguimiento fue muy corto
- No se evaluó la necesidad de retratamiento con RTX transcurridos 9-12 meses
- Los efectos adversos fueron similares en ambos grupos, pero se comparó RTX con CF oral, mucho mas tóxica que CF iv (bolus)

CONCLUSIONS

Rituximab therapy was not inferior to daily cyclophosphamide treatment for induction of remission in severe ANCA-associated vasculitis and may be superior in relapsing disease. (Funded by the National Institutes of Allergy and Infectious Diseases, Genentech, and Biogen; ClinicalTrials.gov number, NCT00104299.)

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

Rituximab in ANCA-Associated Disease

Ronald J. Falk, M.D., and J. Charles Jennette, M.D.

The practical implications of these two studies are substantial. Rituximab might be considered as an option for first-line therapy for induction of remission of ANCA-associated disease. It remains unclear whether rituximab should be used with glucocorticoids alone or in combination with intravenous cyclophosphamide. Cyclophosphamide therapy has a proven track record of inducing sustained remission. At this juncture, the 6-month follow-up of the RAVE trial does not provide an answer to the question of whether anti–B-cell therapy and glucocorticoids will result in a sustained remission. The RAVE trial does provide additional guidance for patients with disease relapse after previous therapy. Here, rituximab was superior to oral cyclophosphamide for the induction of remission in relapsing disease.

Effects of Duration of Glucocorticoid Therapy on Relapse Rate in Antineutrophil Cytoplasmic Antibody–Associated Vasculitis: A Meta-Analysis

MICHAEL WALSH,[1] PETER A. MERKEL,[2] ALFRED MAHR,[2] AND DAVID JAYNE[3]

Arthritis Care & Research

- 13 estudios: 776 pacientes de 8 ensayos randomizados y 207 pacientes de 5 estudios observacionales
- 3 estudios (288 pacientes) con mantenimiento de corticoides a dosis bajas entre 12 y 22 meses (periodo completo de seguimiento)
- 11 estudios con supresión de corticoides durante el periodo de seguimiento entre los 6 y 27 meses: se subdividieron entre dosis 0 de corticoides antes o despues de los 12 meses.

- Resultados meta-regresión análisis:
- 48% de recidivas cuando los corticoides se suprimieron antes de los 12 meses
- 29% de recidivas cuando los corticoides se suprimieron despues de 12 meses
- 14% de recidivas cuando los corticoides no se retiraron durante el periodo de seguimiento (20% si se mantuvieron al menos 12 meses)
- La tasa de recidivas fue 3 veces mayor en los pacientes en los que se suprimieron los corticoides, respecto a los que los mantuvieron

Conclusion. **Studies with longer courses of GC in AAV are associated with fewer relapses. These results have implications for study design and outcome assessment in clinical trials of AAV.**

Our study also suggests that early withdrawal of GC is associated with more relapses of AAV and implies that low-dose GC for greater than 12 months would provide a demonstrable benefit to patients.

Mortality in Behçet's Disease

D. Saadoun,[1] B. Wechsler,[1] K. Desseaux,[2] D. Le Thi Huong,[1] Z. Amoura,[1] M. Resche-Rigon,[2] and P. Cacoub[1]

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Table 1. Characteristics of the patients with Behçet's disease (BD) and comparison between patients who died and those who remained alive*

Parameter	All (n = 817)	Died (n = 41)	Alive (n = 776)
Age at diagnosis, mean ± SD years	31.5 ± 10.5	34.8 ± 11.9	31.4 ± 10.4
Male sex	541 (66.2)	38 (92.7)	503 (64.8)
Ethnic origin			
Europe	365 (44.7)	15 (36.6)	350 (45.1)
North Africa	336 (41.1)	19 (46.3)	317 (40.8)
Africa	73 (8.9)	4 (9.8)	69 (8.9)
Other	43 (5.3)	3 (7.1)	40 (5.1)
HLA–B5 (n = 642)	259 (40.3)	11/31 (35.5)	300/611 (49.1)
Oral ulceration	812 (99.4)	41 (100)	771 (99.3)
Genital ulceration	568 (69.5)	18 (43.9)	550 (70.8)
Ocular involvement	514 (62.9)	25 (61)	489 (63.0)
CNS involvement	220 (26.9)	15 (36.6)	205 (26.4)
Articular involvement	354 (43.3)	20 (48.8)	334 (43.0)
Venous involvement	301 (36.8)	18 (43.9)	283 (36.5)
Arterial involvement	114 (13.9)	15 (36.6)	99 (12.8)
Number of BD flares, mean ± SD	3.7 ± 2.6	4.0 ± 2.7	3.6 ± 2.7
BD flares ≥5	179 (21.9)	12 (29.3)	167 (21.5)
Immunosuppressants	431 (52.8)	31 (75.6)	400 (51.6)

* Except where indicated otherwise values are the number (%) of patients. CNS = central nervous system.

Table 3. Factors associated with mortality in Behçet's disease (BD)*

Parameter	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age at diagnosis	1.38 (0.6–3.3)	0.49		
Male sex	6.87 (2.1–22.3)	0.001	4.94 (1.5–16.4)	0.007
Geographic origin				
Europe	1			
North Africa	2.48 (0.8–7.4)	0.11		
Africa	1.71 (0.8–3.3)	0.12		
Other	2.45 (0.7–8.5)	0.16		
Number of BD flares	2.47 (0.1–1.6)	0.018	2.37 (1.1–5.1)	0.029
HLA–B5	0.51 (0.2–1.1)	0.07		
Oral ulcerations	0.54 (0.1–2.2)	0.39		
Genital ulcerations	0.41 (0.2–0.7)	0.006	0.49 (0.2–0.9)	0.044
Ocular involvement	0.78 (0.3–1.6)	0.51		
CNS involvement	1.42 (0.8–3.3)	0.42		
Articular involvement	1.02 (0.5–1.9)	0.96		
Venous involvement	1.06 (0.1–2.2)	0.88		
Arterial involvement	3.3 (1.4–7.8)	0.005	2.51 (1.1–5.9)	0.034
Immunosuppressants	2.39 (1.1–4.8)	0.017		

* HR = hazard ratio; 95% CI = 95% confidence interval; CNS = central nervous system.

Causas muerte:

- Afección arterial: aneurismas arteriales pulmonares(3), aneurisma aorta torácica (3), IAM (3), aneurisma aorta abdominal (1), aneurismas cerebrales (1)
- Afección venosa: Budd-Chiari (4), TEP (3)
- Afección SNC (5)

Conclusion. **The overall mortality in our BD cohort was 5% after a median followup of 7.7 years. Male sex, arterial involvement, and the number of flares were associated with mortality in BD.**

Antiplatelet Therapy for the Prevention of Arterial Ischemic Events in Takayasu Arteritis

Alexandre W. S. de Souza, MD, PhD; Natália P. Machado, MD; Vanessa M. Pereira, MD; Anne E. D. Arraes, MD; Edgard T. Reis Neto, MD; Henrique A. Mariz, MD; Emilia Inoue Sato, MD, PhD

Background: Vessel wall inflammation, atherosclerosis and hypercoagulability may be responsible for ischemic events in Takayasu arteritis (TA). No study has evaluated the effect of antiplatelet therapy for the prevention of ischemic events in TA.

Table 1. Demographic and Clinical Data of 48 TA Patients

	Results
Female gender, n (%)	43 (89.6%)
Caucasian, n (%)	29 (60.4%)
Mean age at study end, years	38.0 (95%CI 34.3–41.7)
Mean age at TA diagnosis, years	29.1 (95%CI 26.0–32.2)
Mean disease duration, months	103.5 (95%CI 81.1–125.9)
Mean delay for TA diagnosis, months	37.2 (95%CI 15.8–58.7)
Prednisone, n (%)	43 (89.6%)
Methotrexate, n (%)	43 (89.6%)
Cyclophosphamide, n (%)	15 (31.3%)
Azathioprine, n (%)	10 (20.8%)
Mycophenolate sodium, n (%)	2 (4.2%)
Anti-TNFα agents, n (%)	3 (6.3%)

Estudio retrospectivo observacional

54% pacientes: Takayasu tipo V

Factores riesgo CV: HTA 77.1%, LDL 45.8%, obesidad 16.7%

Table 2. Comparison Between TA Patients With and Without Ischemic Events

	Ischemic event (n=14)	No ischemic event (n=34)	P value
Age at diagnosis, years	30.6±11.9	28.5±10.1	0.699
Female, n (%)	13 (92.9)	30 (88.2)	1.000
Caucasian, n (%)	7 (50.0)	22 (64.7)	0.344
Time since TA symptoms, months	118.9±101.3	148.8±107.8	0.324
Time since TA diagnosis, months	74.3±52.7	115.5±82.7	0.123
Delay in diagnosis, months	44.7±87.7	34.2±68.4	0.616
Antiplatelet agents, n (%)	2 (14.3)	28 (82.4)	<0.0001*
Median aspirin dose, mg/day	350	200	0.082
Anticoagulant therapy, n (%)	3 (21.4)	3 (8.8)	0.339
Prednisone, n (%)	12 (85.7)	31 (91.2)	0.621
Immunosuppressive drugs, n (%)	12 (85.7)	32 (94.1)	0.569
Statin therapy, n (%)	8 (57.1)	13 (38.2)	0.230
Risk factors for CVD, n (%)	13 (92.9)	31 (91.2)	1.000
Advanced age, n (%)	1 (7.1)	2 (5.9)	1.000
Tobacco use, n (%)	2 (14.3)	2 (5.9)	0.569
Systemic hypertension, n (%)	12 (85.7)	25 (73.5)	0.469
Low HDL-C, n (%)	2 (14.3)	0 (0.0)	0.081
Mean HDL-C, mg/dl	60.33±20.43	54.81±13.44	0.466
High LDL-C, n (%)	7 (50.0)	15 (44.1)	0.710
Diabetes, n (%)	1 (7.1)	3 (8.8)	1.000
Obesity, n (%)	2 (14.3)	6 (17.6)	1.000
Family history of premature CVD, n (%)	0 (0.0)	1 (2.9)	1.000
Mean number of risk factors for CVD, mean ± SD	2.08±0.86	1.77±0.80	0.290
Deaths, n (%)	3 (21.4)	0 (0.0)	0.021*

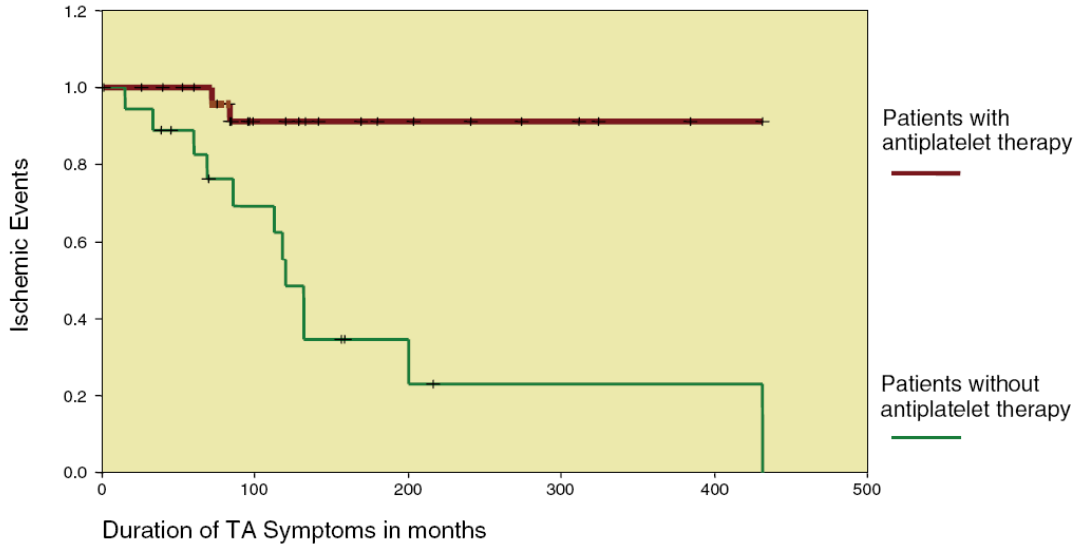

Figure. Differences between Takayasu arteritis (TA) patients with or without antiplatelet therapy by Kaplan-Meier curve.

Conclusions: Antiplatelet therapy is associated with a lower frequency of ischemic events in patients with TA.
(*Circ J* 2010; **74:** 1236–1241)