Con il patrocinio di

Associazione Italiana Pneumologi Ospedalieri

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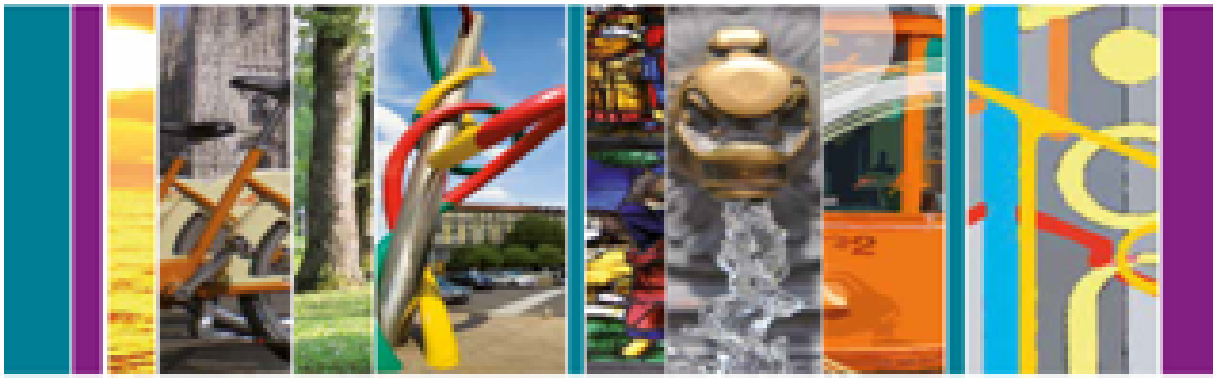
PNEUMOLOGIA 2016

Milano, 16 – 18 giugno 2016 · Centro Congressi Palazzo delle Stelline



PNEUMOLOGIA 2016

Milano, 16 – 18 giugno 2016 · Centro Congressi Palazzo delle Stelline

Nuove terapie nelle vasculiti ANCA-associate

Gina Gregorini

UO Nefrologia ASST Spedali Civili di Brescia

The New England
Journal of Medicine

Volume 285 DECEMBER 30, 1971 Number 27

EFFECT OF CYCLOPHOSPHAMIDE UPON THE IMMUNE RESPONSE IN WEGENER'S GRANULOMATOSIS

ANTHONY S. FAUCI, M.D., SHELDON M. WOLFF, M.D., AND JOHN S. JOHNSON, M.D.

Abstract Nine patients with Wegener's granulomatosis were studied before and after treatment with cyclophosphamide alone. The study was undertaken to determine any immunologic abnormalities associated with the disease, to observe the effect of cyclophosphamide on the clinical course, as well as on the immune response in man, and to observe any correlation between clinical response and immunosuppression. Untreated patients had elevated mean serum IgA levels of 470 as compared with 200 mg per 100 ml in normal controls and elevated mean parotid-fluid secretory IgA levels of 4.7 as compared with 1.8 mg per 100 ml in normal controls. Seven of nine patients receiving cyclophosphamide had undetectable humoral and delayed hypersensitivity responses to a new antigenic stimulus, and five of the seven retained previously established delayed hypersensitivity. A favorable clinical response to cyclophosphamide and immunosuppression appeared to be correlated.

Fauci AS et al, N Engl J Med 1971; 285: 1493-6

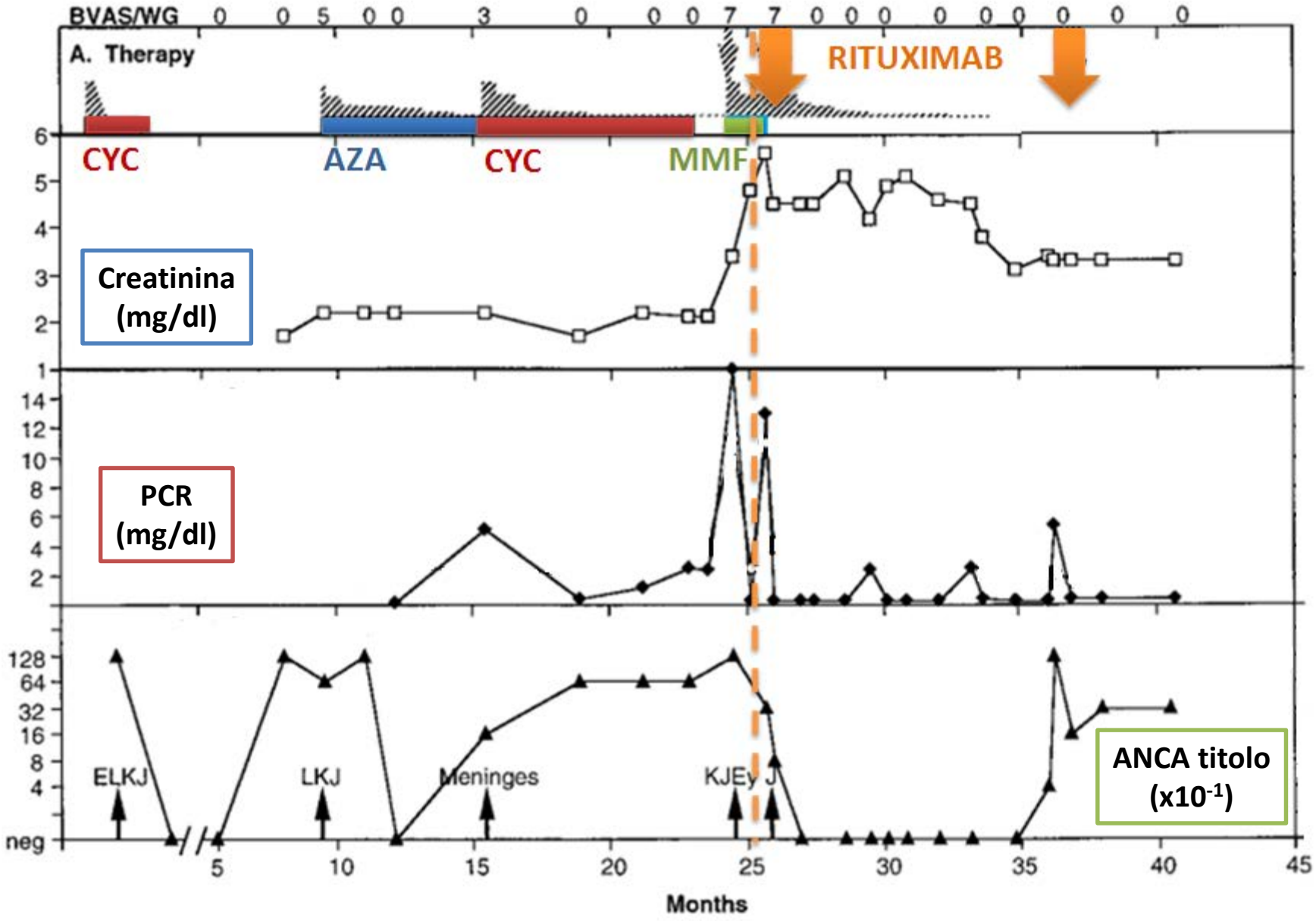
Response of Wegener's Granulomatosis to Anti-CD20 Chimeric Monoclonal Antibody Therapy

Ulrich Specks, Fernando C. Fervenza, Thomas J. McDonald, and Marie C. E. Hogan

- ✓ We report on the successful, compassionate use of the anti-CD20 chimeric monoclonal antibody rituximab in a patient with chronic, relapsing cytoplasmic antineutrophil cytoplasmic antibody (cANCA)-associated Wegener's granulomatosis (WG). The patient initially responded to treatment with glucocorticoids and cyclophosphamide. However, bone marrow toxicity during cyclophosphamide treatment of a relapse precluded its further use. Azathioprine and mycophenolate mofetil treatment had failed to maintain remission of the WG, and methotrexate was contraindicated… Because the patient's 5-year course was characterized by close correlation of cANCA levels with disease activity, selective elimination of cANCA was deemed a treatment option for his latest relapse. He was given 4 infusions of 375 mg/M2 of rituximab and high-dose glucocorticoids. Complete remission was associated with the disappearance of B lymphocytes and cANCA

Specks U et al, Arthritis Rheum 2001; 44: 2836-40

Specks U et al, Arthritis Rheum 2001; 44: 2836-40


BVAS/WG 0 0 5 0 0 3 0 0 0 7 7 0 0 0 0 0 0 0 0 0
A. Therapy
RITUXIMAB
CYC
AZA
CYC
MMF
Creatinina (mg/dl)
PCR (mg/dl)
ANCA titolo (x10-1)
ELKJ
LKJ
Meninges
KJEy J
Months

Razionale per l'utilizzo del Rituximab nelle AAV

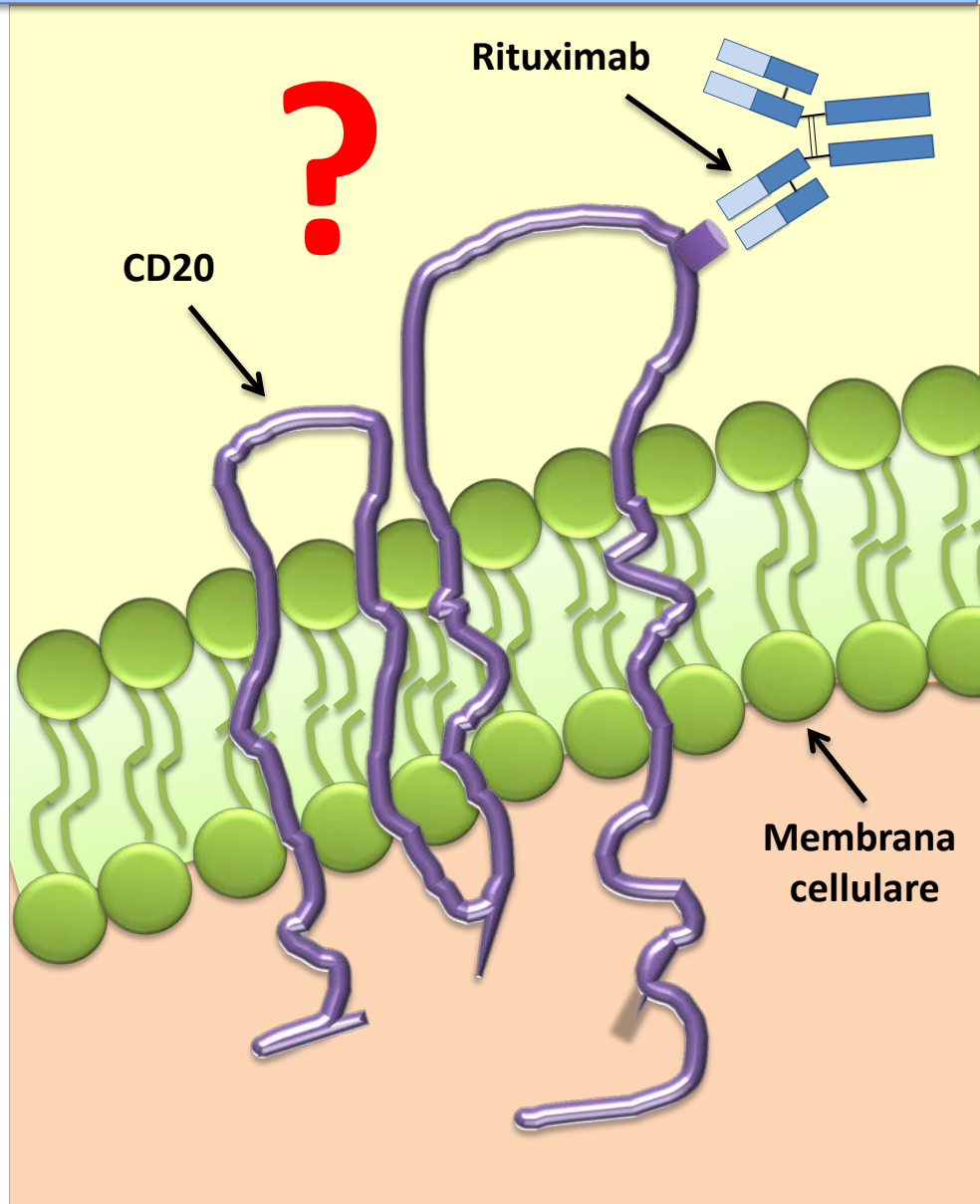
- ✓ ANCA bio-indicatori di GPA / MPA / EGPA
- ✓ ANCA fortemente coinvolti nella patogenesi delle lesioni vasculitiche
- ✓ Efficacia della acuta rimozione degli ANCA con plasma-exchange
- ✓ La ciclofosfamide sopprime l'attivazione e la proliferazione delle cellule B ed è efficace nel trattamento delle AAV.
- ✓ Cellule B autoreattive sono presenti nelle lesioni granulomatose della GPA.

CD20

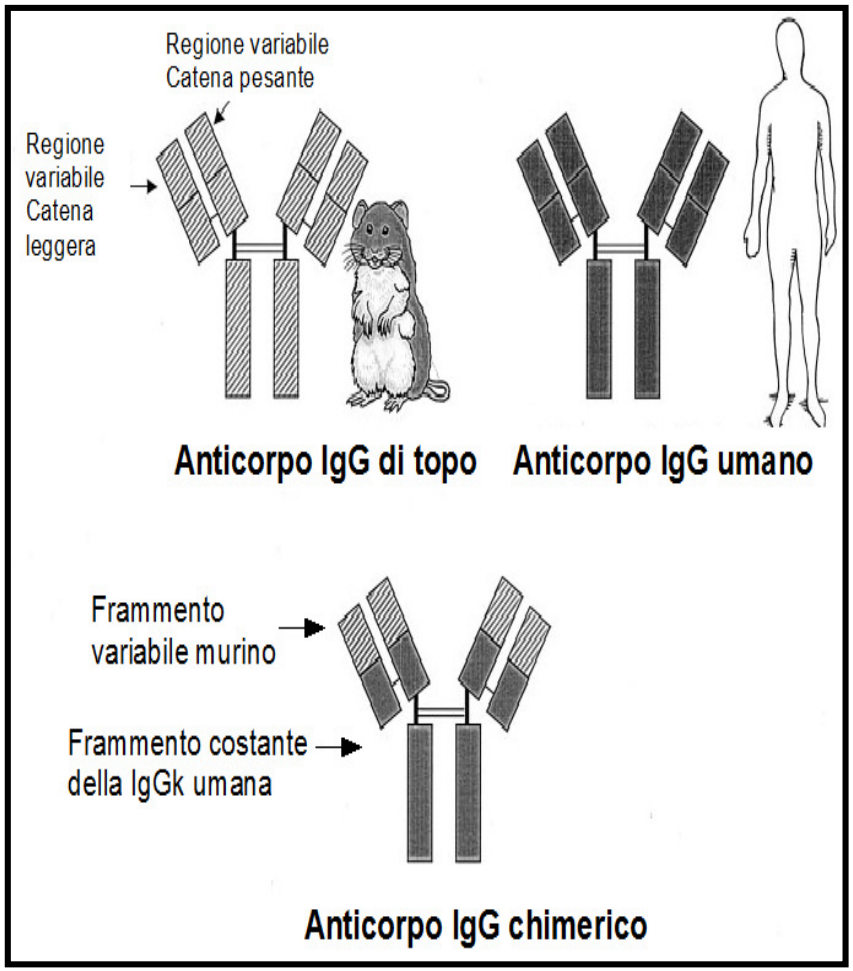
- ✓ Proteina transmembrana di circa 35 kD
- 4 regioni transmembrana;
- un loop extracellulare di 44 aa;
- terminali amino e carbossilico intracitoplasmatici.

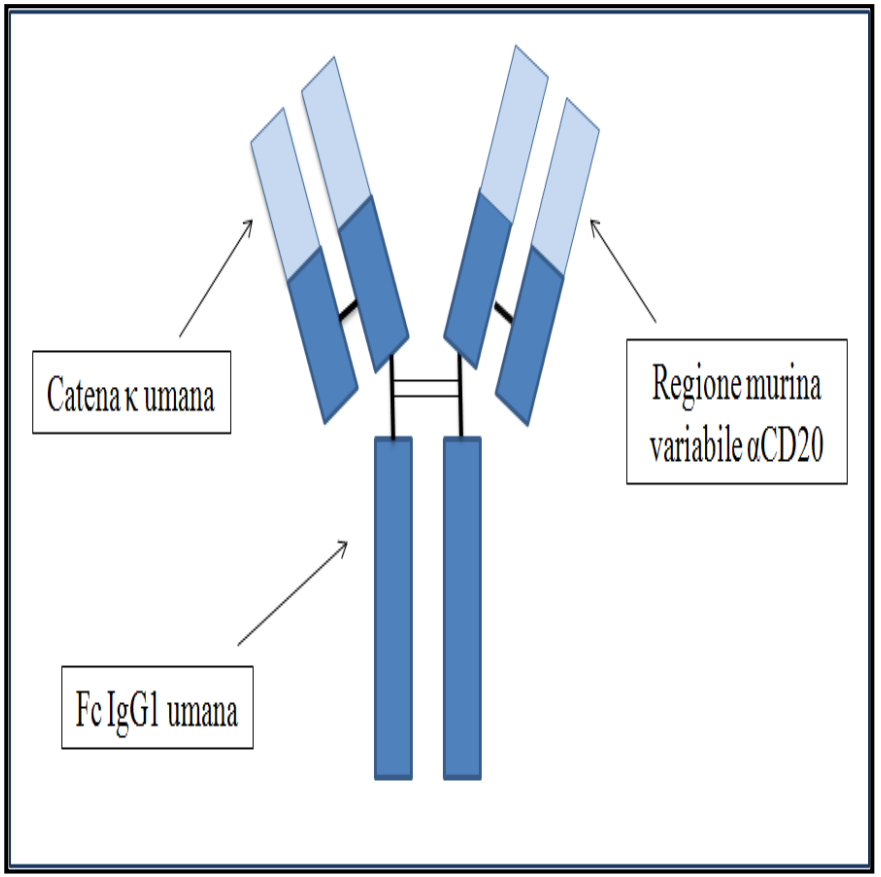
- ✓ Funzione di regolazione della proliferazione cellulare.

- ✓ Il legame del Rituximab al CD20 blocca la progressione del ciclo cellulare dei linfociti B dalla fase G1 alla fase S.

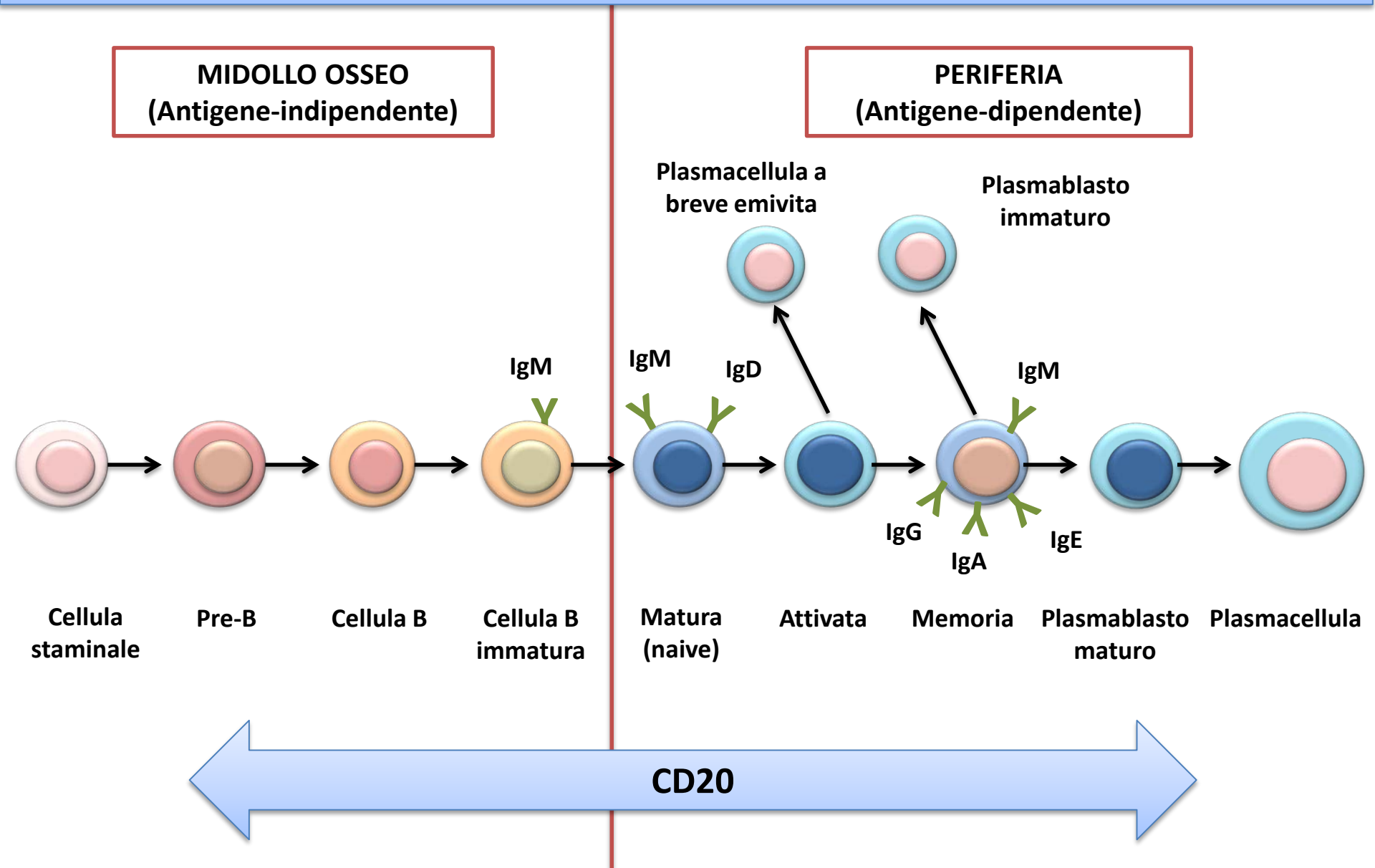


Struttura del Rituximab

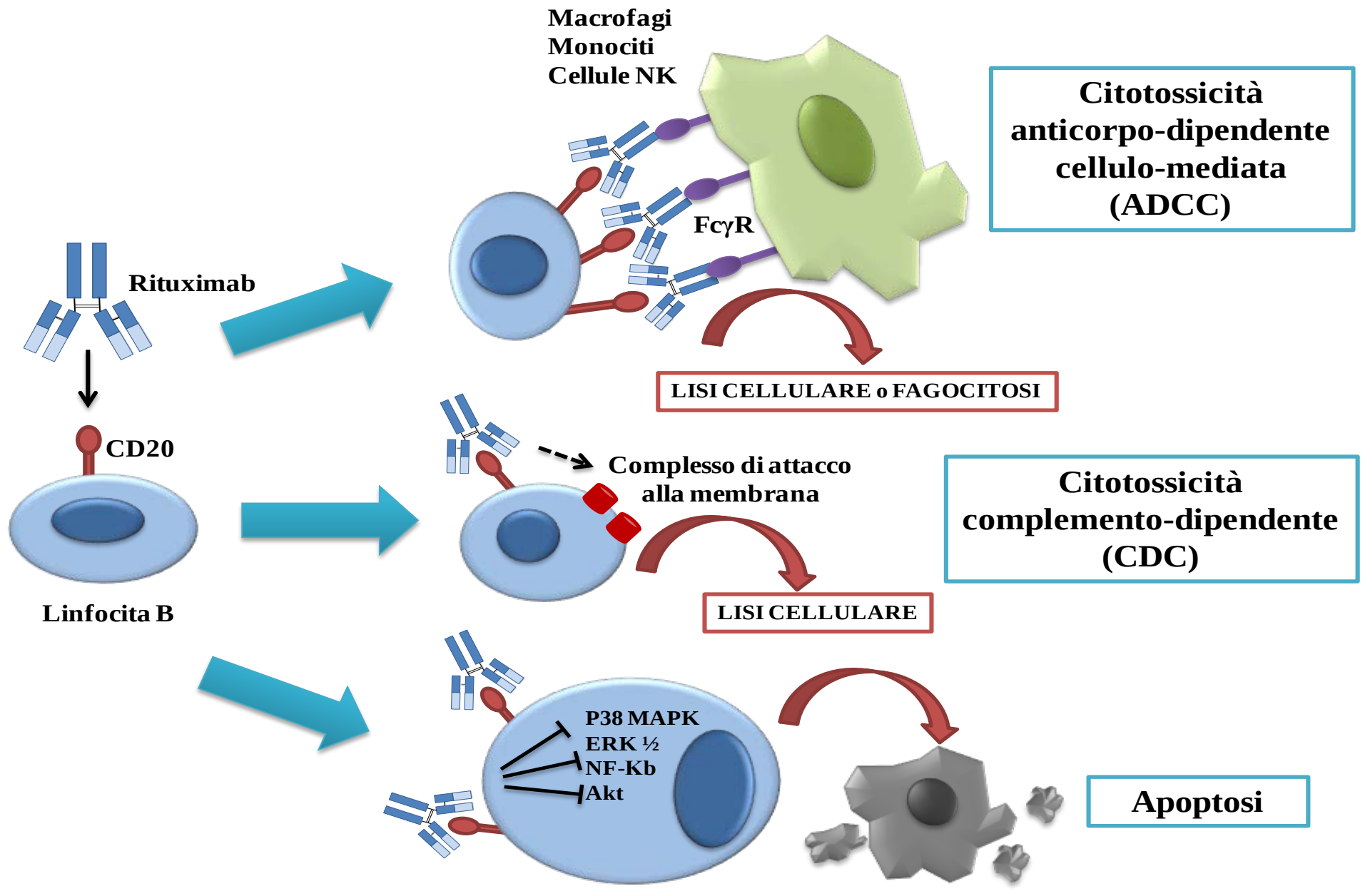




Espressione del CD20



I tre meccanismi principali della deplezione dei linfociti B ad opera del Rituximab

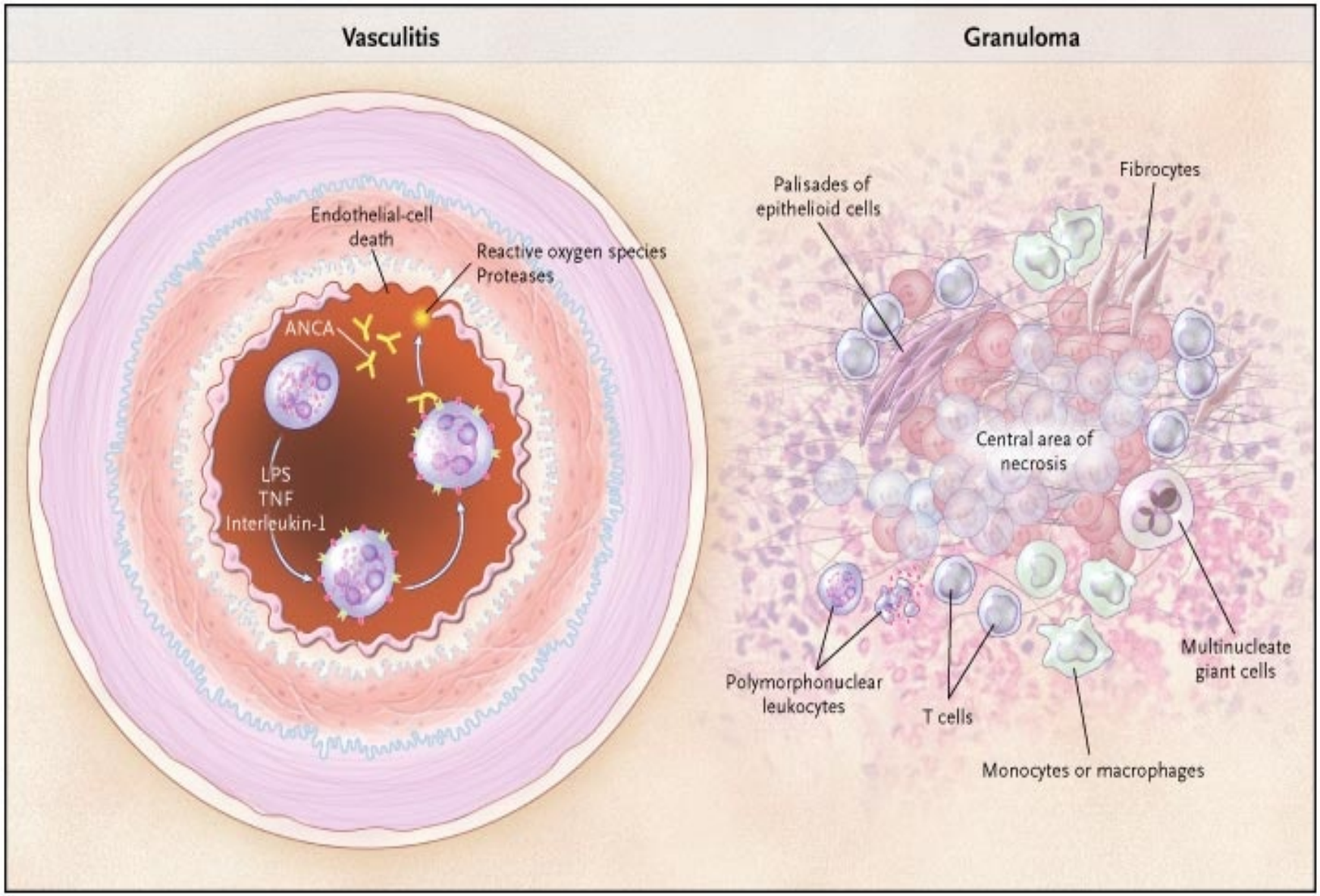


Potenziali meccanismi di resistenza o di suscettibilità alla deplezione da parte di anticorpi monoclonali anti-CD20 (modificata da Leandro 2013)

Correlata a linfocita B ed antigene	Mancata espressione del CD20
	Modulazione/endocitosi dell'antigene (CD20)
	Composizione della membrana lipidica
	Espressione di proteine regolatrici del complemento
Correlata a caratteristiche dell'ospite	Polimorfismi del recettore FcγRIIIa
	Espressione del recettore FcγRIIb
	Polimorfismi del C1q
	Esaurimento dei meccanismi citotossici (es. complemento)

Effetto del Rituximab

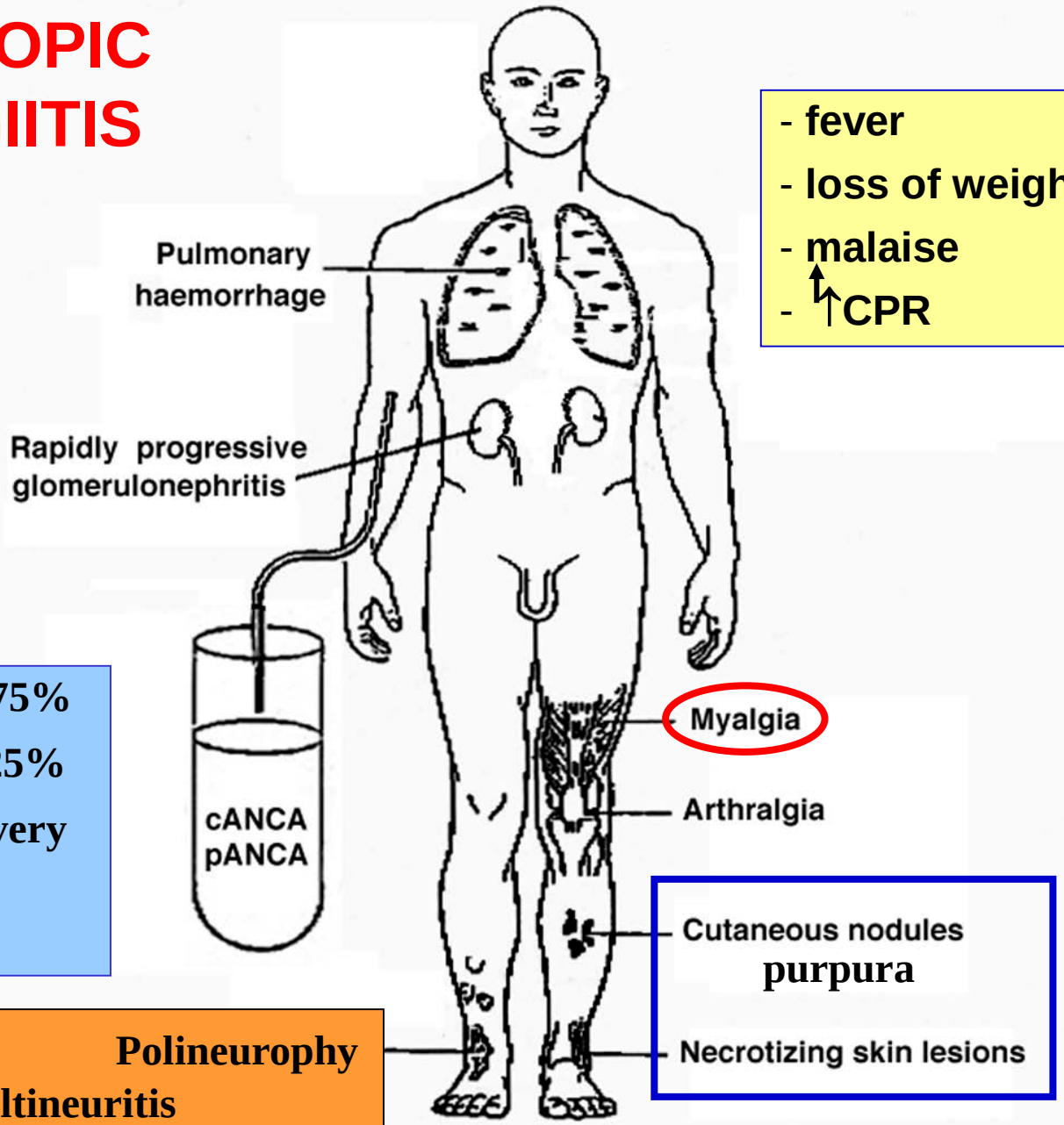
- Rapida e completa (>99%) deplezione delle cellule B del sangue periferico.
- Deplezioni di grado più variabile ed incomplete sono state documentate in alcuni pz con malattie autoimmuni > in AR e LES
- La deplezione delle cellule B residenti in tessuti diversi dal sangue periferico è stata molto meno studiata. Evidenza da molti studi di deplezione incompleta e con molte variazioni inter-individuali
  - nelle sinovie di articolazioni colpite in pz con AR
  - nelle ghiandole salivari in pz con Sjogren
  - nei reni espiantati



Tratto da: The Spectrum of Wegener's Granulomatosis and Disease Relapse Paul A. Bacon, M.D. N Engl J Med 352:330-332, January 27, 2005

MICROSCOPIC POLYANGIITIS

- fever
- loss of weight
- malaise
- ↑↑CPR

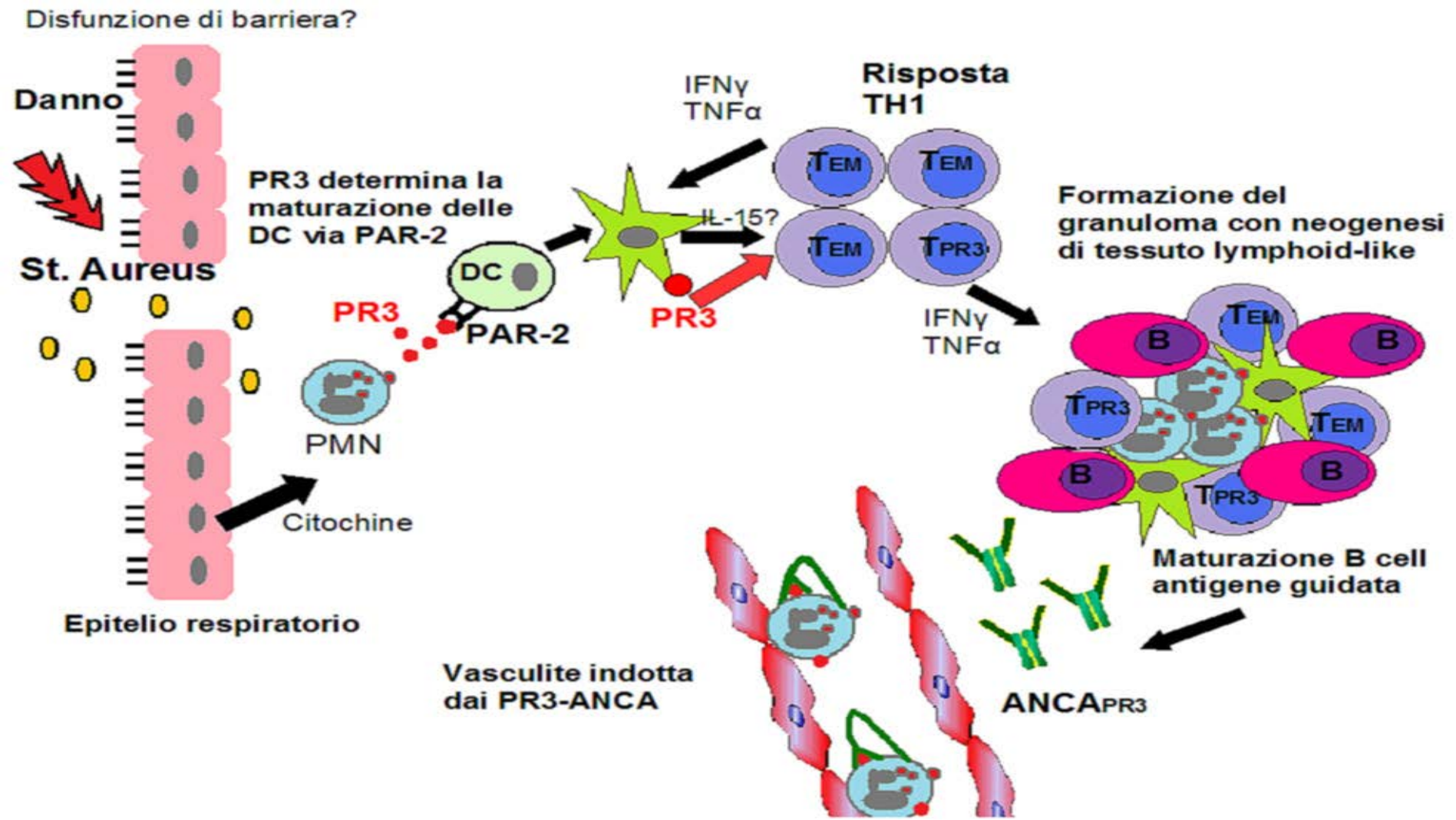


P-ANCA/antiMPO 75%

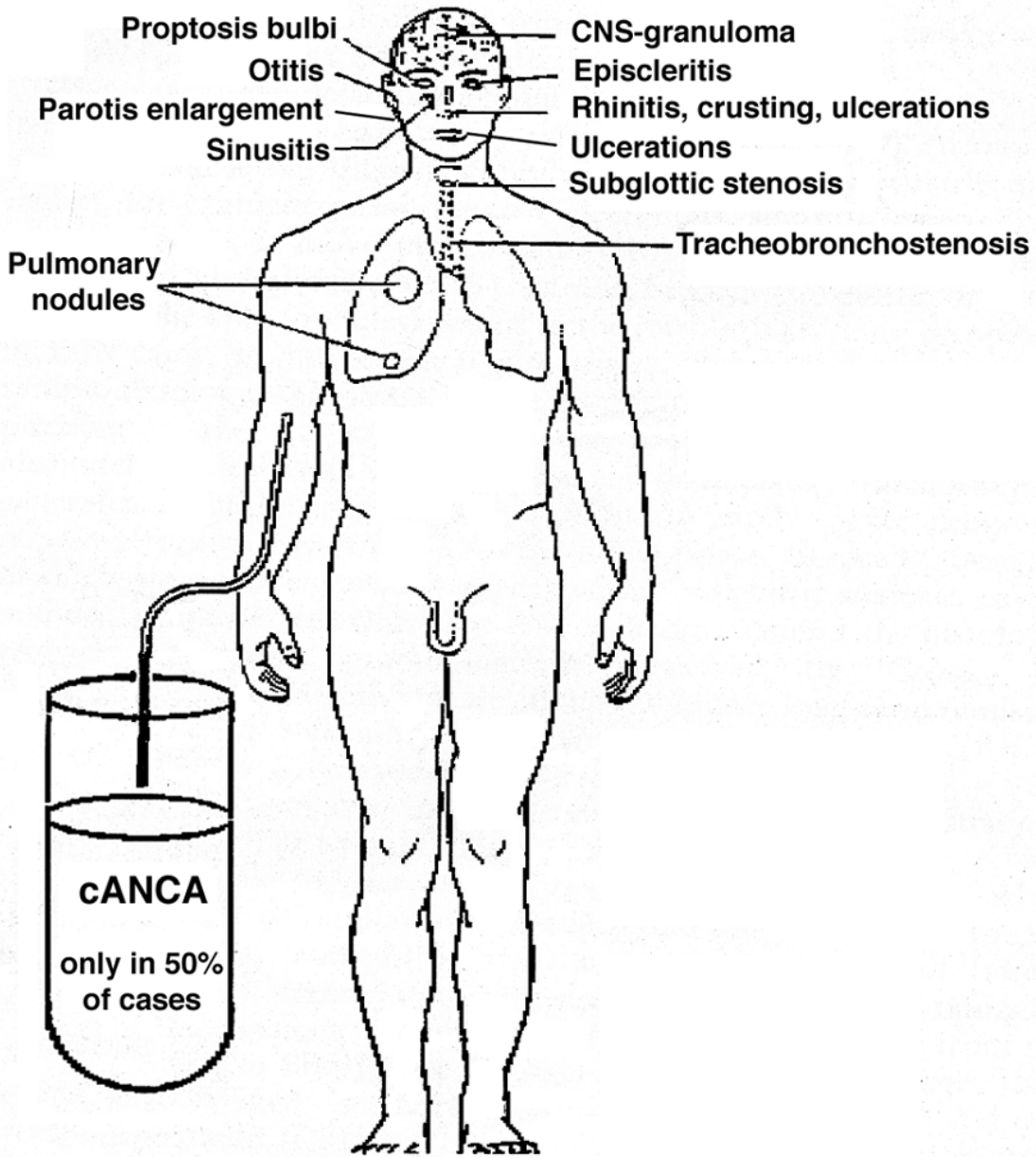
C-ANCA/antiPR3 25%

P-ANCA+ (ANA -): very few

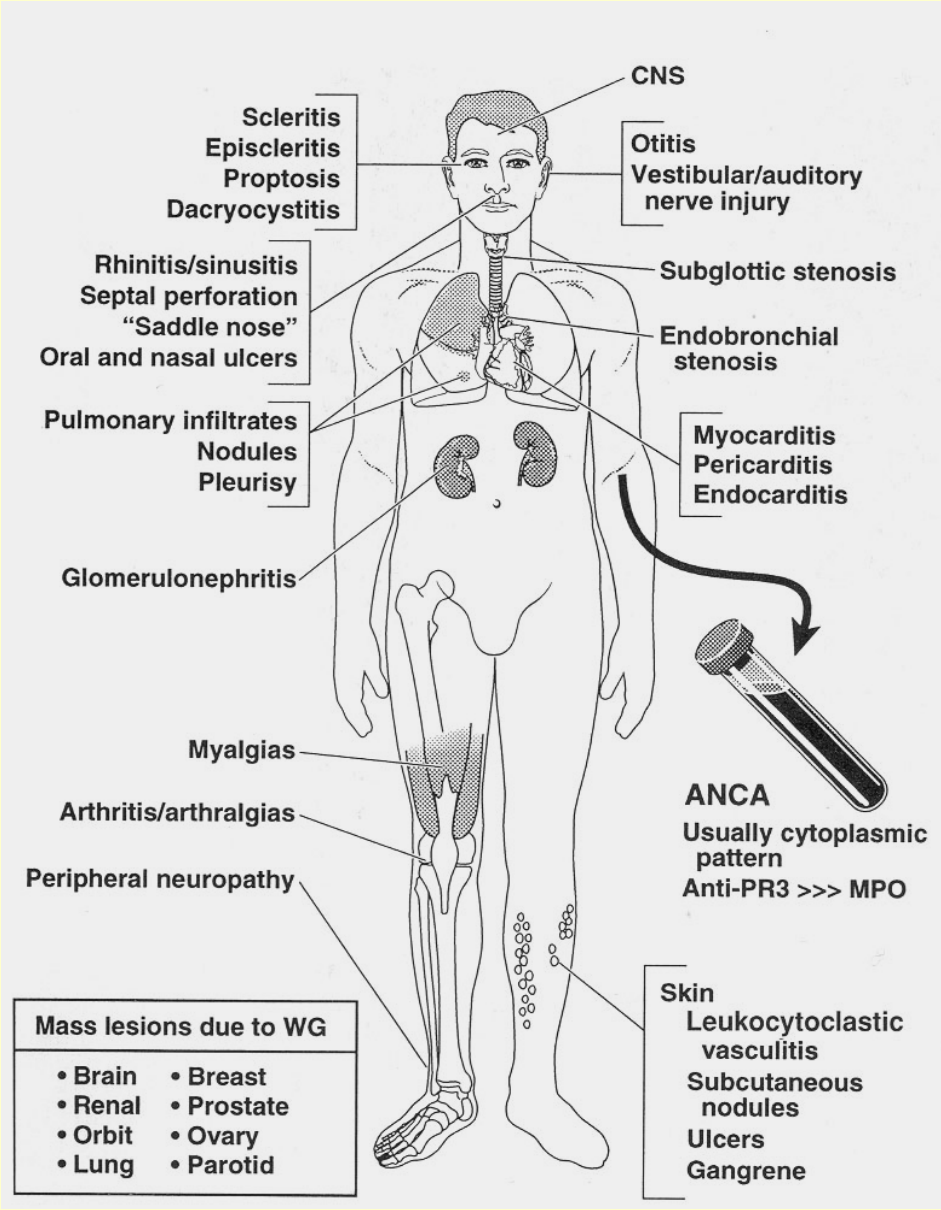
ANCA neg ?



Un agente esogeno determina un'infiammazione a livello delle vie respiratorie,liberazione della proteinasi 3(PR3) e attivazione delle cellule dendritiche (DC) tramite il recettore attivato dalle proteasi 2 (PAR-2).
Le cellule dendritiche inducono una risposta tipo Th1 specifica per PR3 con formazione di un granuloma ricco di aree lymphoid-like. Nel granuloma le cellule B CD20+ subiscono un processo di maturazione antigene dipendente trasformandosi in plasmacellule produttrici di PR3 ANCA che scatenano una vasculite del microcircolo



Wegener's Granulomatosis: localized form



Wegener's Granulomatosis: generalized form

Quali le differenze le sotto il profilo della tossicità

- Rituximab provoca una deplezione selettiva dei linfociti B CD-20 positivi

- Ciclofosfamide è un agente alchilante che si lega al DNA ed induce un effetto citotossico più ampio e meno specifco

RAVE

Rituximab for ANCA-Associated Vasculitis

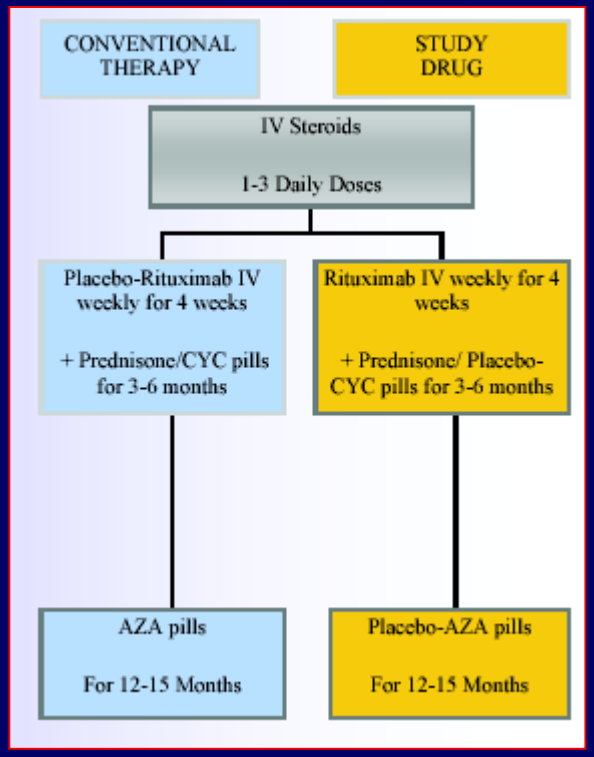
Sponsored by The National Institute of Allergy and Infectious Disease and The Immune Tolerance Network

EUDRACT 2005-003610-15

RITUXVAS Clinical Trial Protocol
EUDRACT number: 2005-003610-15, REC reference:05/Q1604/153

European Vasculitis Study Group (EUVAS) Trial

Version 1b: 15th November 2005



INIZIO
(criteri di inclusione)

↓

RANDOMIZZAZIONE
(braccio sperimentale 33; braccio di controllo 11)

RITUXIMAB 375 mg/m2 ev x4
CICLOFOSFAMIDE 15 mg/kg ev settimana 0 e 2
METILPREDNISOLONE 1 gr ev
PREDNISOLONE PO

CICLOFOSFAMIDE EV (3-6 mesi)
METILPREDNISOLONE 1 gr ev
PREDNISOLONE PO

↓

REMISSIONE/MANTENIMENTO
AZA 2 mg/kg

FINE DELLO STUDIO DOPO 2 ANNI

RAVE vs RITUXVAS

	RAVE	RITUXVAS
Disegno dello studio		
Disegno generale	Randomizzato, doppio cieco, non-inferiorità, follow-up 18 mesi	Randomizzato, open-label, superiorità, follow-up 24 mesi
Regime di induzione nel gruppo di controllo	CYC per os per 3-6 mesi Steroide ad alte dosi con progressiva riduzione e sospensione a 6 mesi	CYC e.v. per 3-6 mesi Steroide ad alte dosi scalato a 5 mg di prednisolone a 6 mesi
Regime di induzione nel gruppo RTX	RTX 375 mg/m^2 x 4 Steroide ad alte dosi scalato e poi sospeso a 6 mesi	RTX 375 mg/m^2 x 4 2 dosi di CYC e.v. Steroide ad alte dosi scalato a 5 mg di prednisolone a 6 mesi
Regime di mantenimento nel gruppo di controllo	AZA per os	AZA per os, basse dosi di steroide
Regime di mantenimento nel gruppo RTX	Nessuno	Basse dosi di steroide
Plasmaferesi	Non consentita	Uso opzionale consentito
Endpoint primario	Remissione a 6 mesi (con aderenza alla sospensione dello steroide)	Remissione sostenuta per 6 mesi entro 12 mesi

Rituximab nella terapia di induzione delle AAV

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 15, 2010 VOL. 363 NO. 3

RAVE

Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis

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.)

Spiera, M.D.,
S.,
D.,
hao, M.D.,
R.N., B.S.N.,
le, Ph.D.,
netta, M.D.,
Seetha, M.D.,
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*

RITUXVAS

Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis

Rachel B. Jones, M.R.C.P., M.D., Jan Willem C
Raashid Luqmani, D.M., F.R.C.P., F.R.C.P.(E.), Matthew
Caroline O. Savage, Ph.D., F.R.C.P., F.Med.Sci., Ma
Pieter van Paassen, M.D., Ph.D., Dorothy W
Kerstin Westman, M.D., Ph.D., and David R.W. Jayn

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.)

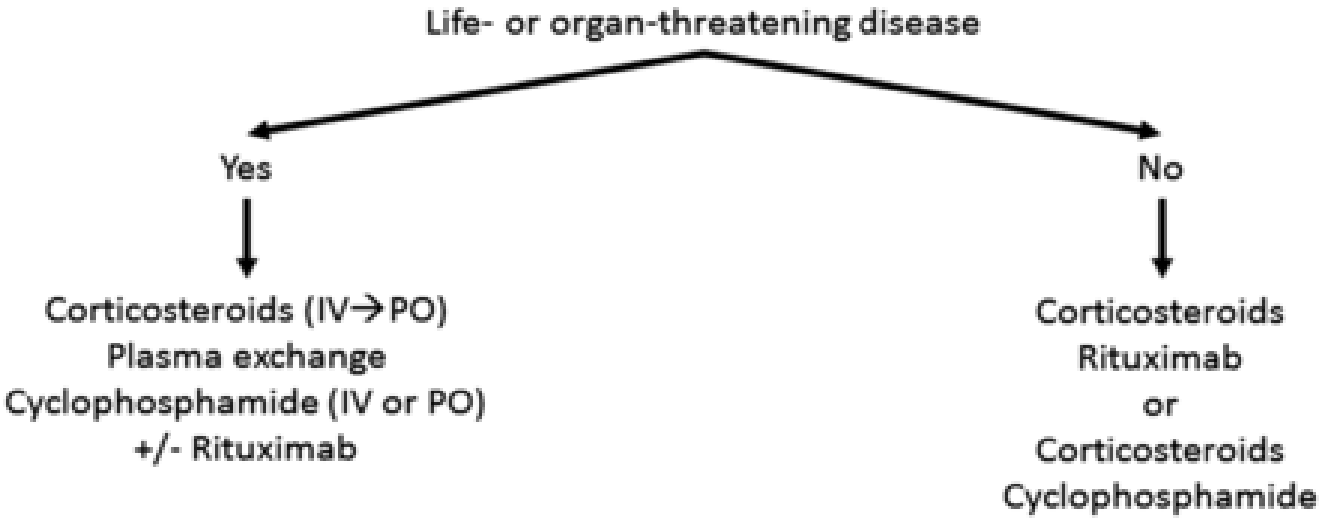
RAVE vs RITUXVAS

	RAVE	RITUXVAS
Caratteristiche della popolazione		
Pazienti	197 (99 RTX, 98 CYC)	44 (33 RTX, 11 CYC)
Tipo di AAV	GPA 148 (75%) MPA 48 (25%)	GPA 22 (50%) MPA 16 (36%) limitata al rene 6 (14%)
Malattia all'esordio/alla recidiva	All'esordio 96 (48%) Alla recidiva 101 (52%)	All'esordio 44 (100%)
Vasculite renale	130 (66%) esclusi se creatinina >4 mg/dl	44 (100%), nessun criterio di esclusione renale
Emorragia alveolare diffusa	Esclusa	
Necessità di dialisi all'esordio	0 (0%)	9 (20%)
ANCA-positivi	196 (99%)	44 (100%)

Understanding the Role of Rituximab in ANCA GN: Regressing toward the Mean

William F. Pendergraft III and Ronald J. Falk
University of North Carolina Kidney Center, Division of Nephrology and Hypertension, Department of Medicine, School of Medicine, University of North Carolina, Chapel Hill, North Carolina

Remission induction regimen for ANCA glomerulonephritis



The ongoing PEXIVAS plasma exchange trial (NCT00987389) is recruiting 700 patients, including those with dialysis dependence. PEXIVAS permits the use of either cyclophosphamide or rituximab for remission induction, so it may expand knowledge of rituximab's efficacy in this subgroup

Nephrol Dial Transplant (2015) 30: 1075–1081
doi: 10.1093/ndt/gfv216
Advance Access publication 21 May 2015

ndt
Nephrology Dialysis Transplantation

Polar Views in Nephrology

Con: Should all patients with anti-neutrophil cytoplasmic antibody-associated vasculitis be primarily treated with rituximab?

Andreas Kronbichler and David R. W. Jayne

Vasculitis and Lupus Clinic, Addenbrooke's Hospital, Cambridge CB2 0QQ, UK

We propose that cyclophosphamide is still first-line therapy in induction of remission due to high remission rates and long-standing experience with regard to the safety profile. Rituximab-associated adverse events are comparable with those observed following cyclophosphamide therapy, and together with the higher costs and similar clinical efficacy rituximab should be considered as second-line treatment modality.

Opponent's comments

Ulrich Specks

Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester,

I still can advocate cyclophosphamide as initial induction therapy only for newly diagnosed MPO-ANCA positive patients without contraindications for the drug and whose disease is too severe to warrant a treatment trial with mycophenolate mofetil. For newly diagnosed PR3-ANCA positive patients, all relapsing patients with severe disease, and patients with refractory disease, rituximab is the preferred initial induction agent. Finally, there are currently no valid data that support the benefit of the addition of cyclophosphamide or other immunosuppressive agents.

Moderator's view: Should all patients with ANCA-associated vasculitis be primarily treated with rituximab?

Vladimir Tesar

Department of Nephrology, First Faculty of Medicine, Charles University in Prague and General University Hospital in Prague, Prague, Czech Republic

In my opinion, rituximab can be used in some newly diagnosed patients with AAV, but with the available information it is too early to use it as a first-line treatment in all new AAV patients. Undoubtedly, within several years we will have much more data to base our choice of primary treatment of newly diagnosed AAV more on evidence than mostly on opinion.

RITUXIMAB as a first-line treatment

- ❑ in young patients desiring to get pregnant following remission of vasculitis
- ❑ in patients with concomitant severe infection or at higher risk of infections
- ❑ inpatients with concomitant malignancy
- ❑ in patients with myelodysplasia

Analisi della letteratura

Casi di GW con manifestazioni granulomatose trattati con RTX:	**59**	
Remissione completa	**45/59**	**(76%)**
Remissione parziale	**5/59**	**(8%)**
Resistenti	***9/59**	**(16%)**

*7/9 erano granulomi retro-orbitari; 5 da un'unica casistica (Arise) con 6/8 fallimenti.

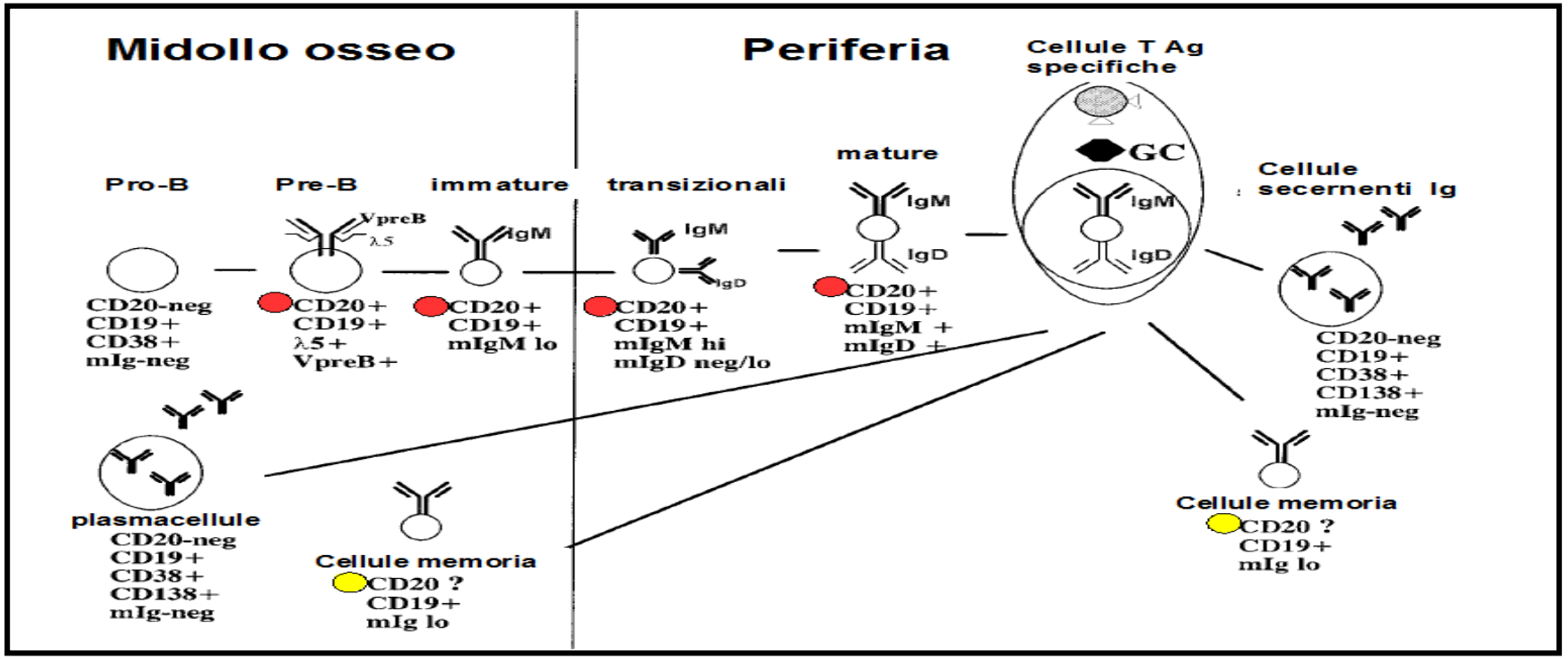
Possibili spiegazioni dei risultati negativi in controtendenza:
- follow-up troppo breve (1 mese) per le forme granulomatose
- somministrazione del RTX mensile invece che settimanale
- subset di patologia estremamente resistente

5 dei pazienti resistenti hanno poi risposto ad un trattamento con azatioprina ev. suggerendo una possibile efficacia del RTX in sinergismo con l'AZA.

Nelle casistiche analizzate: 11 granulomi retro-orbitari:4 remissione 7 resistenti

La ripopolazione delle cellule B del sangue periferico

- inizia usualmente dopo 6-9 mesi ma questo tempo è variabile in base a severità della deplezione, iniziale clearance del farmaco, capacità rigenerative del midollo, età? altre caratteristiche individuali?
- questo è il processo oggi al centro della attenzione. Si ricercano nelle caratteristiche della ricomparsa delle diverse cellule B "biomarcatori" predittori di recidiva di malattia



Identificati tre marcatori

1. associazione tra ripopolazione con B linfociti naive e ridotto rischio di recidiva (Emery, 2015) "Relapse rates at 12 and 18 months were 0% and 14% with naïve repopulation at 6 months, and 31% and 54% without naïve repopulation".
2. ripopolazione con basso numero di linfociti B regolatori CD5+ più precoce recidiva di malattia (O ' Bunch D, 2015) After B cell depletion, patients who repopulated with a low or decreasing percentage of $CD5^+$ B cells and were on low maintenance immunosuppression had a shorter time to relapse than patients on similar levels of immunosuppression with normalised $CD5^+$ B cells or patients with similarly low $CD5^+$
3. ripopolazione con predominanti linfociti B della memoria e basso numero di linfociti B naïve e relapse (Smith R,2015)" in a cohort of frequently relapsing pts, at 4 months after RTX , a lower proportion of naïve B cells and a tendency to greater proportion of memory B cells in the low number of circulating B cells, is predictive of relapse.

Cinetica di ripopolazione dei linfociti B

Ricomparsa dei linfociti B

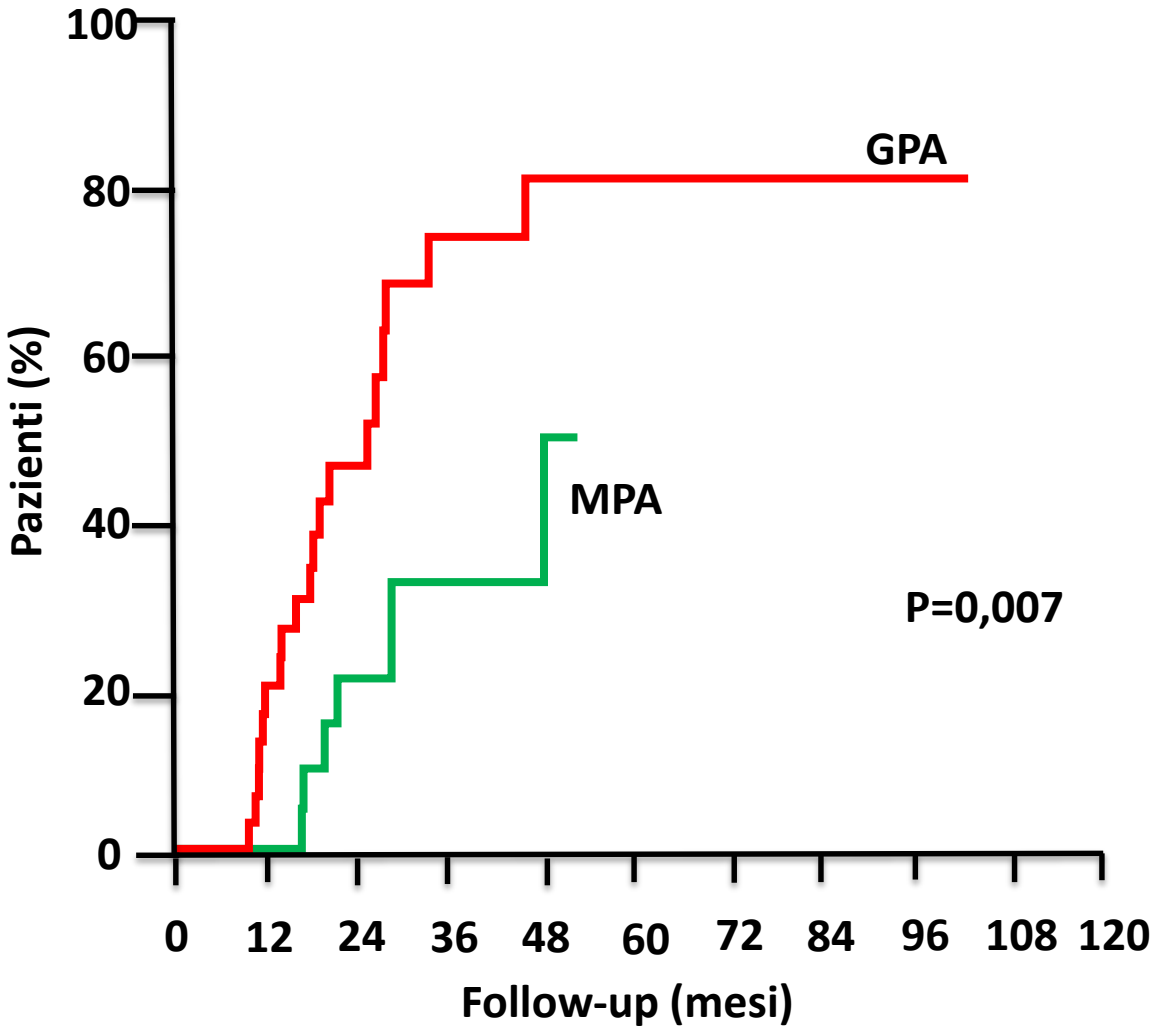
✓La ricomparsa dei linfociti B veniva definita dalla presenza di un numero di cellule compreso tra 10 e 69/µl.

✓I dati sulla cinetica di ricomparsa dei CD19 erano disponibili per 74 pazienti.

✓Tra questi, la ricomparsa si verificava in soli 26 pazienti (19 GPA, 6 MPA, 1 EGPA), dopo un tempo medio di 20,3±10,5 mesi (range 9,8-47,5).

✓In nessun paziente si osservava ricomparsa dei linfociti B prima di 9 mesi dal trattamento con Rituximab.

Ricomparsa dei linfociti B



Ricostituzione dei linfociti B

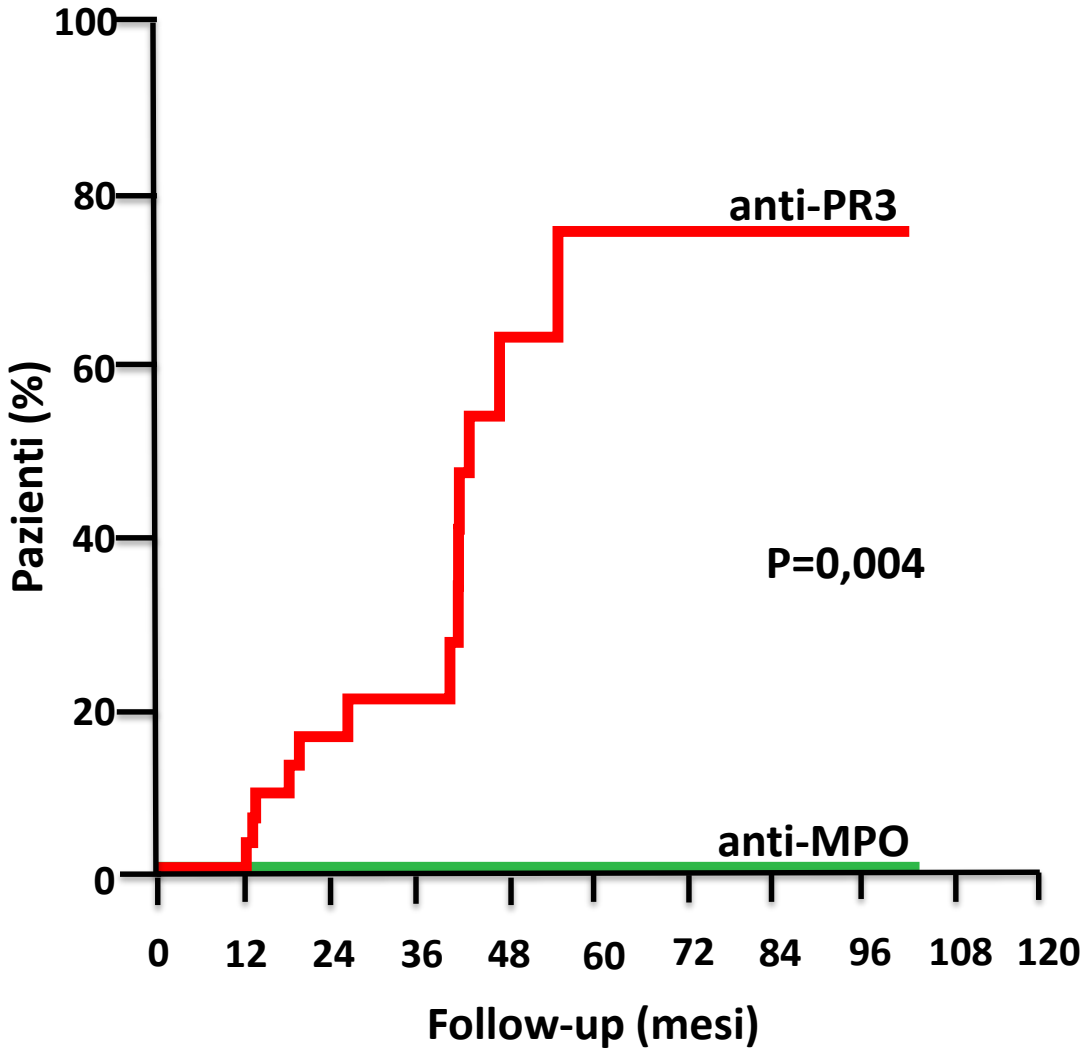
✓La ricostituzione era definita dalla presenza di un numero di cellule > 69/µl.

✓Nel corso del follow-up, la ricostituzione dei linfociti B si verificava in 19 su 92 pazienti.

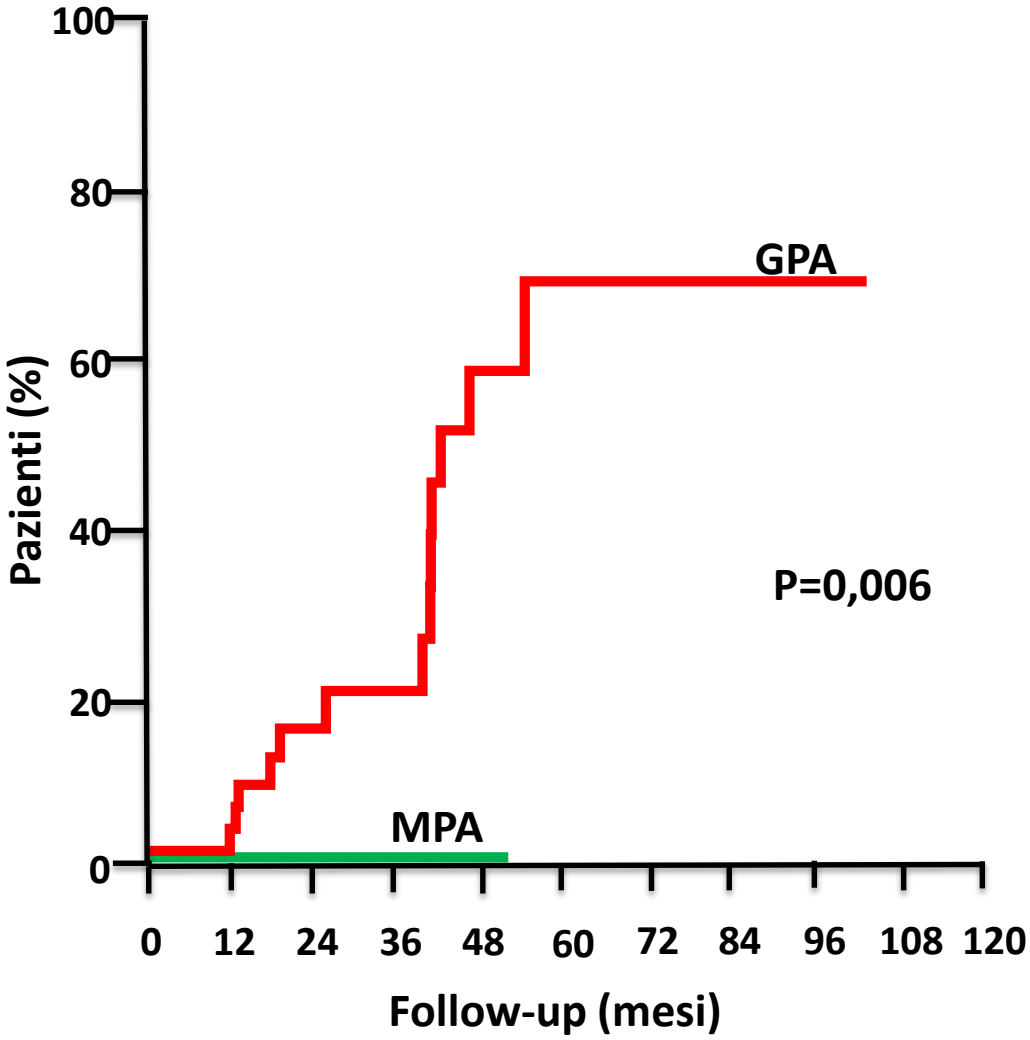
✓I dati riguardanti la cinetica di ricostituzione dei linfociti B erano disponibili per 83 pazienti.

✓Nei 13 pazienti di questo gruppo che andava incontro a ricostituzione dei linfociti B, questa si verificava dopo un tempo medio di 28,9±16,4 mesi (range 12-54,1).

Ricostituzione dei linfociti B



Ricostituzione dei linfociti B



Persistente deplezione linfocitaria dopo il primo ciclo di trattamento con Rituximab in pazienti affetti da vasculiti ANCA-associate

Salviani C°, Gregorini G°, Delbarba E°, Jeannin G°, Regazzoli A*, Cancarini G°

° UO Nefrologia; * Laboratorio di Analisi Chimico-Cliniche; Azienda Ospedaliera Spedali Civili di Brescia

120 pazienti affetti da AAV all'esordio di malattia o ad una recidiva hanno ricevuto il primo ciclo di trattamento con Rituximab tra Gennaio 2006 e Maggio 2015 . Sono stati inclusi in questo studio solo i pazienti con follow-up >12 mesi. In accordo alla letteratura, la deplezione linfocitaria è stata definita come numero di CD19 <10 cell/mm^3.

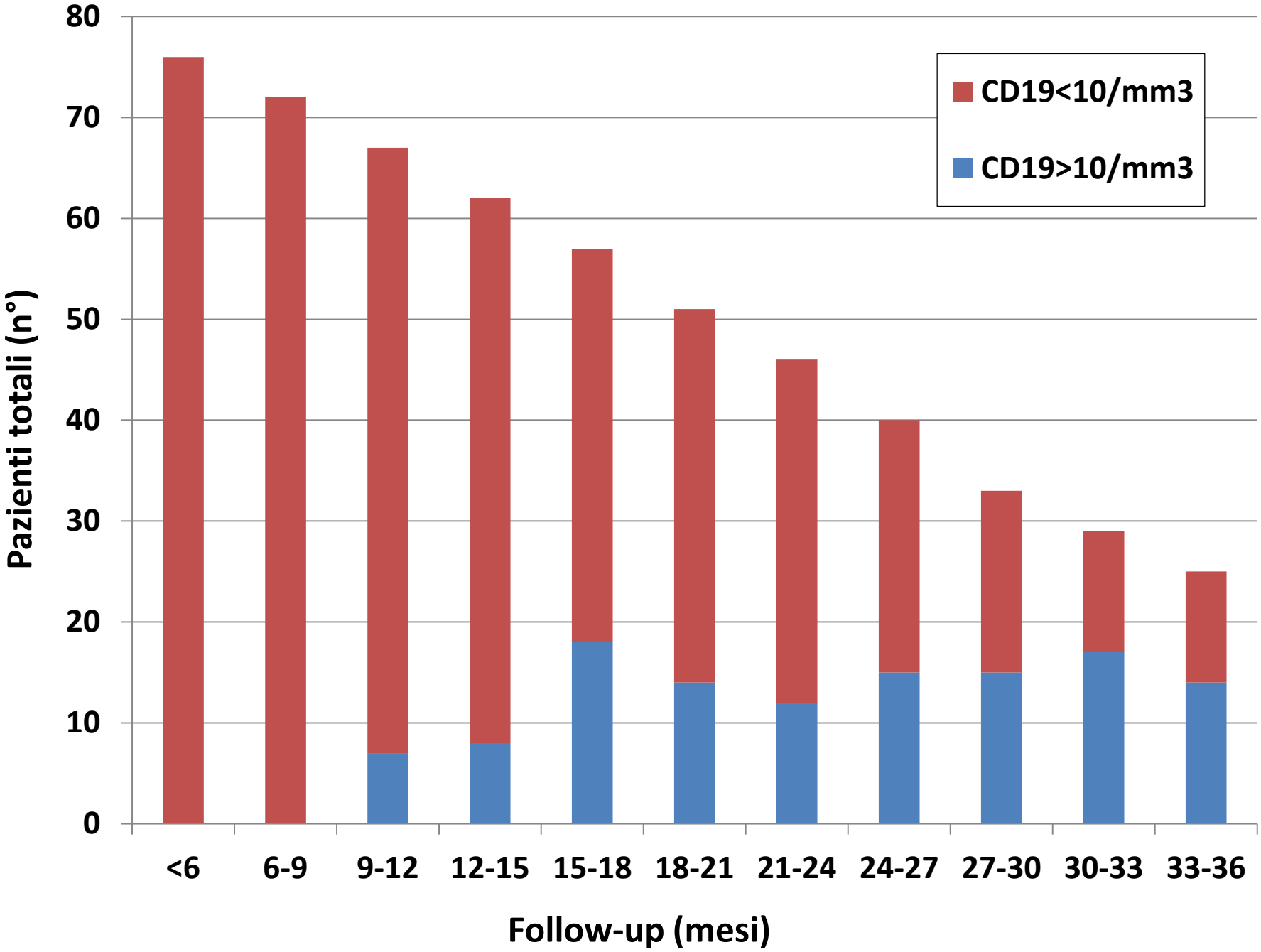
	GPA	MPA	EGPA	Totale
N° pazienti	38	36	2	76
Età media±SD	52,3±18,7	70±13,4	69±1,4	61,4±17,1
M/F	20/18	15/21	1/1	36/40
ANCA:				
anti-MPO	6	33	1	40
anti-PR3	28	3	1	32
negativi	4	0	0	4
Pazienti trattati:				
all'esordio	8	27	1	36
a una recidiva	30	9	1	40

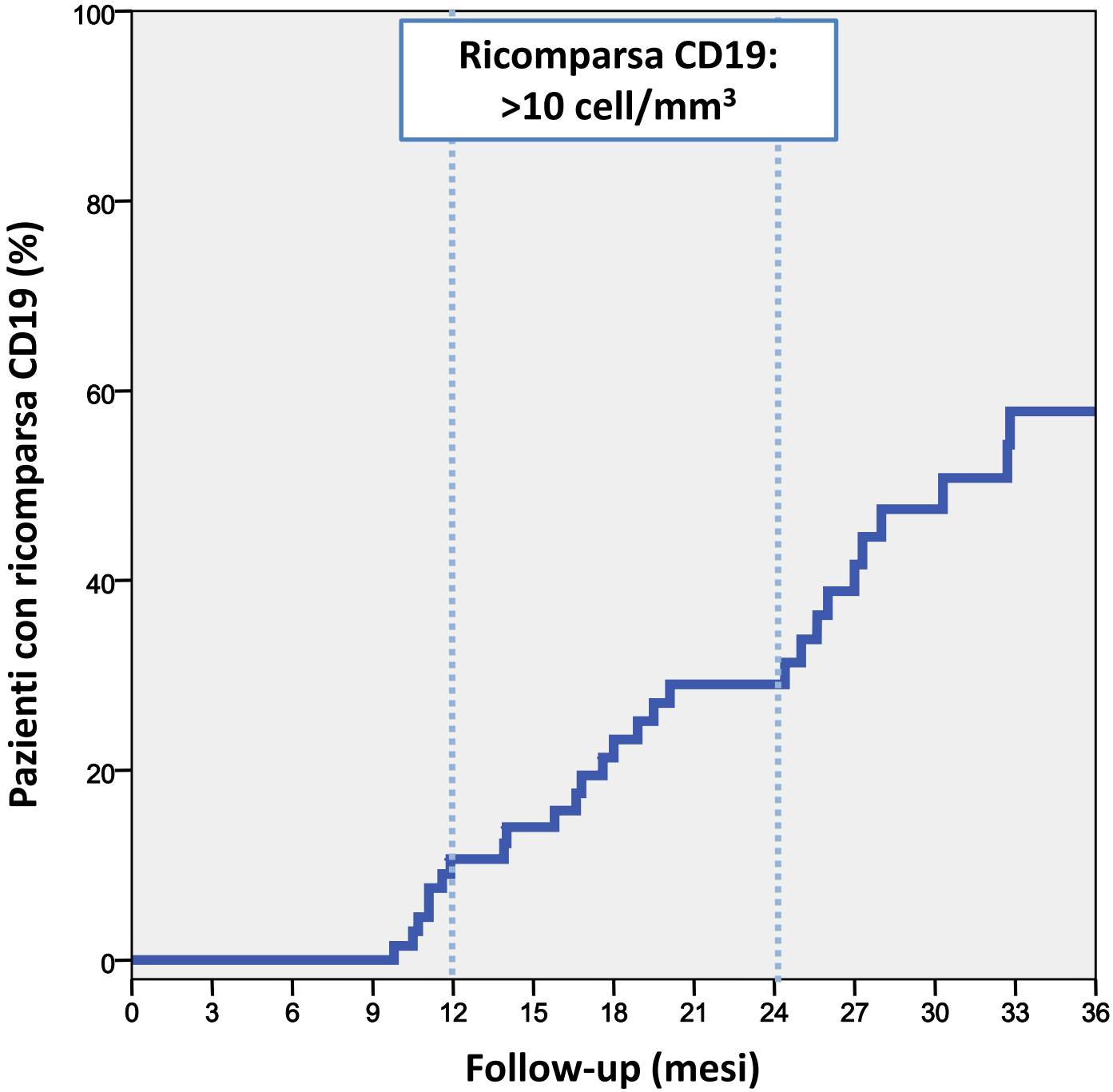
TERAPIE CONCOMITANTI

	GPA	MPA	EGPA	Totale
Plasmaferesi	3	10	1	14
Boli di steroide	3	9	1	13
Steroide per os	38	36	2	76

TERAPIE SUCCESSIVE

	GPA	MPA	EGPA	Totale
Steroide per os	38	36	2	76
Methotrexate	24	2	1	27
Azatioprina	3	5	0	8

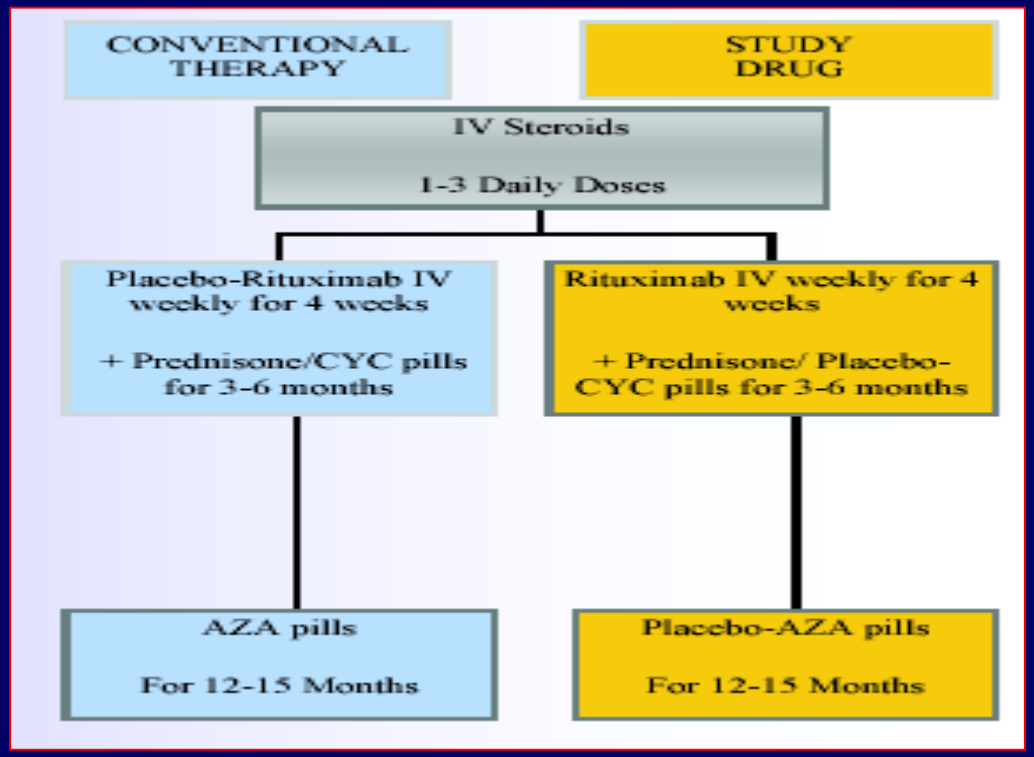

80
70
60
50
40
30
20
10
0
Pazienti totali (n°)
CD19<10/mm3
CD19>10/mm3
<6
6-9
9-12
12-15
15-18
18-21
21-24
24-27
27-30
30-33
33-36
Follow-up (mesi)


Ricomparsa CD19:
>10 cell/mm³
Pazienti con ricomparsa CD19 (%)
100
80
60
40
20
0
0
3
6
9
12
15
18
21
24
27
30
33
36
Follow-up (mesi)

RAVE

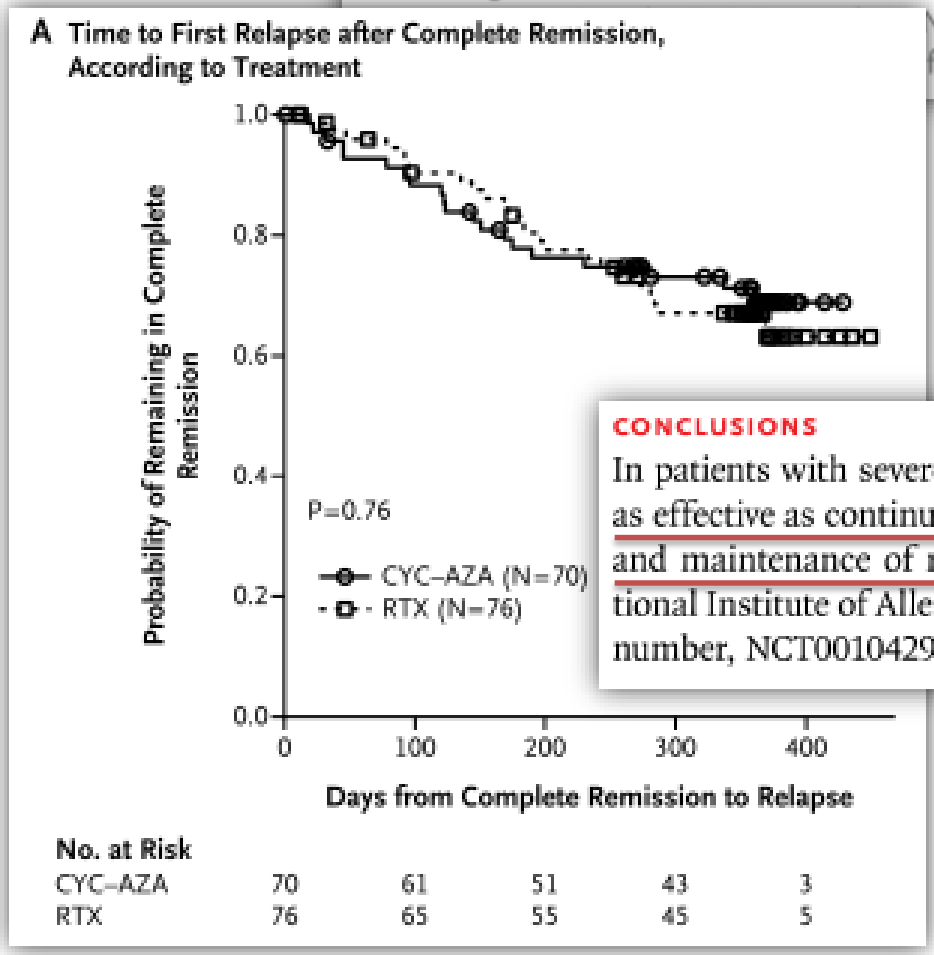
Rituximab for ANCA-Associated Vasculitis

Sponsored by The National Institute of Allergy and Infectious Disease and The Immune Tolerance Network



Efficacy of Remission-Induction Regimens for ANCA-Associated Vasculitis

Ulrich Specks, M.D., Peter A. Merkel, M.D., M.P.H., Philip Seo, M.D., Robert Spiera, M.D., 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., Barri J. Fessler, M.D., Linna Ding, M.D., Ph.D., Lisa Viviano, R.N., Nadia K. Tchao, M.D., Deborah J. Phippard, Ph.D., Adam L. Asare, Ph.D., Noha Lim, Ph.D., David Ikle, Ph.D., Brett Jepson, M.S., Paul Brunetta, M.D., Nancy B. Allen, M.D., Fernando C. Fervenza, M.D., Ph.D., Duvuru Geetha, M.D., Karina Keogh, M.B., B.Ch., 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., Mark Mueller, B.S., C.C.R.P., N., Kathleen Mieras, C.C.R.P., for the RAVE-ITN Research Group*

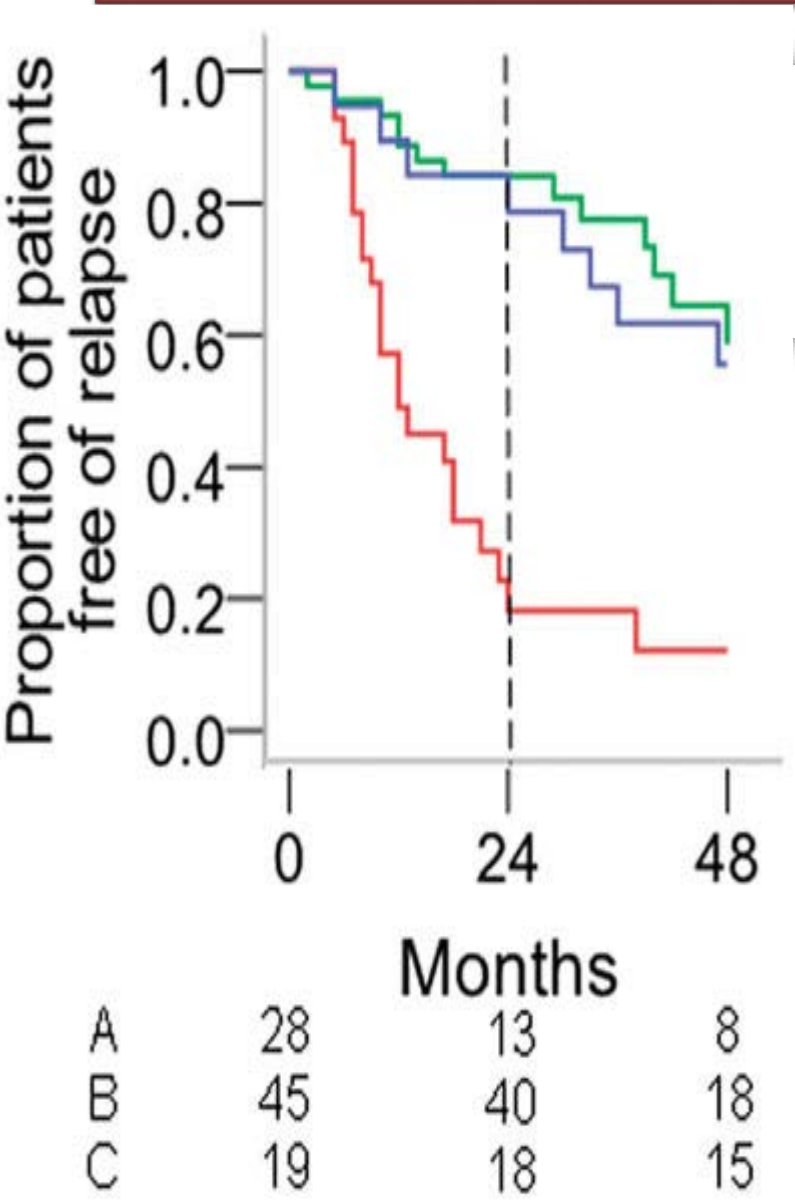


CONCLUSIONS

In patients with severe ANCA-associated vasculitis, a single course of rituximab was as effective as continuous conventional immunosuppressive therapy for the induction and maintenance of remissions over the course of 18 months. (Funded by the National Institute of Allergy and Infectious Diseases and others; RAVE ClinicalTrials.gov number, NCT00104299.)

N Engl J Med 2013;369:417-27

Rituximab nella terapia di mantenimento delle AAV



Rituximab for Remission Maintenance in Relapsing Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

Rona M. Smith,[1] Rachel B. Jones,[1] Mary-Jane Guerry,[1] Simona Laurino,[1] Fausta Catapano,[1] Afzal Chaudhry,[1] Kenneth G. C. Smith,[2] and David R. W. Jayne[1]

group A : 28 received rituximab induction therapy (4 infusions of 375 mg/m(2) or 2 infusions 1 gm) and further rituximab only if there was a clinical relapse

group B : Forty-five patients received 2 doses of 1 gm each for remission induction and then routine re-treatment for 2 years (1 gm every 6 months) (total of 6 gm)

group C : 19 of 28 patients in group A switched to routine re-treatment, either for treatment of a relapse (15 of 19 patients) or for maintenance of remission (4 of 19 patients)

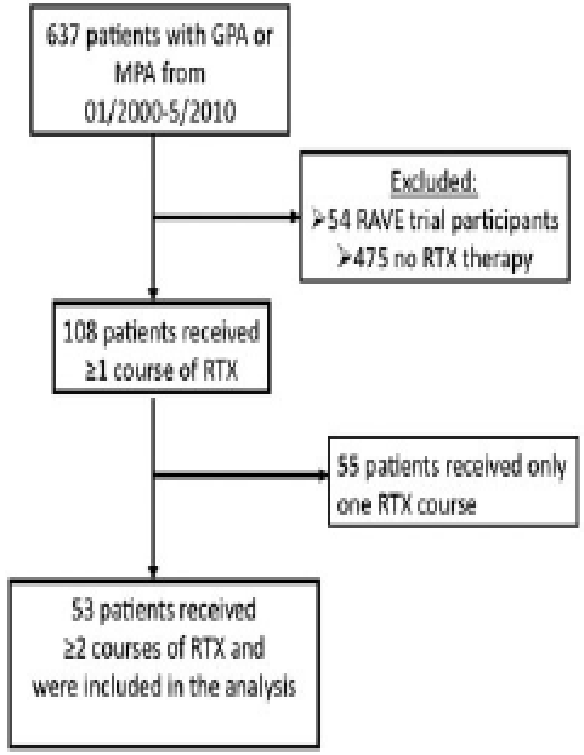
Artritis Rheum. 2012 Nov;64(11):3760-9

Rituximab nella terapia di mantenimento delle AAV

Rituximab for Remission Induction and Maintenance in Refractory Granulomatosis With Polyangiitis (Wegener's)

Ten-Year Experience at a Single Center

Rodrigo Cartin-Ceba,[1] Jason M. Golbin,[2] Karina A. Keogh,[1] Tobias Peikert,[1] Marta Sánchez-Menéndez,[3] Steven R. Ytterberg,[1] Fernando C. Fervenza,[1] and Ulrich Specks[1]



Fifty-three patients with refractory GPA received at least 2 courses of RTX to treat GPA relapses or to maintain remission. All but1 patient had antineutrophil cytoplasmic antibodies(ANCA) against proteinase 3 (PR3). These patients received a median of 4 courses of RTX (IQR 3–5); all had depletion of B cells, and the median time to return of B cells was 8.5 months (IQR 6–11 months). All observed relapses occurred after reconstitution of Bcells and were accompanied or preceded by an increase in ANCA levels, except for the 1 ANCA-negative patient…

RTX appeared to be effective and safe for the induction and maintenance of remission in patients with chronic relapsing GPA

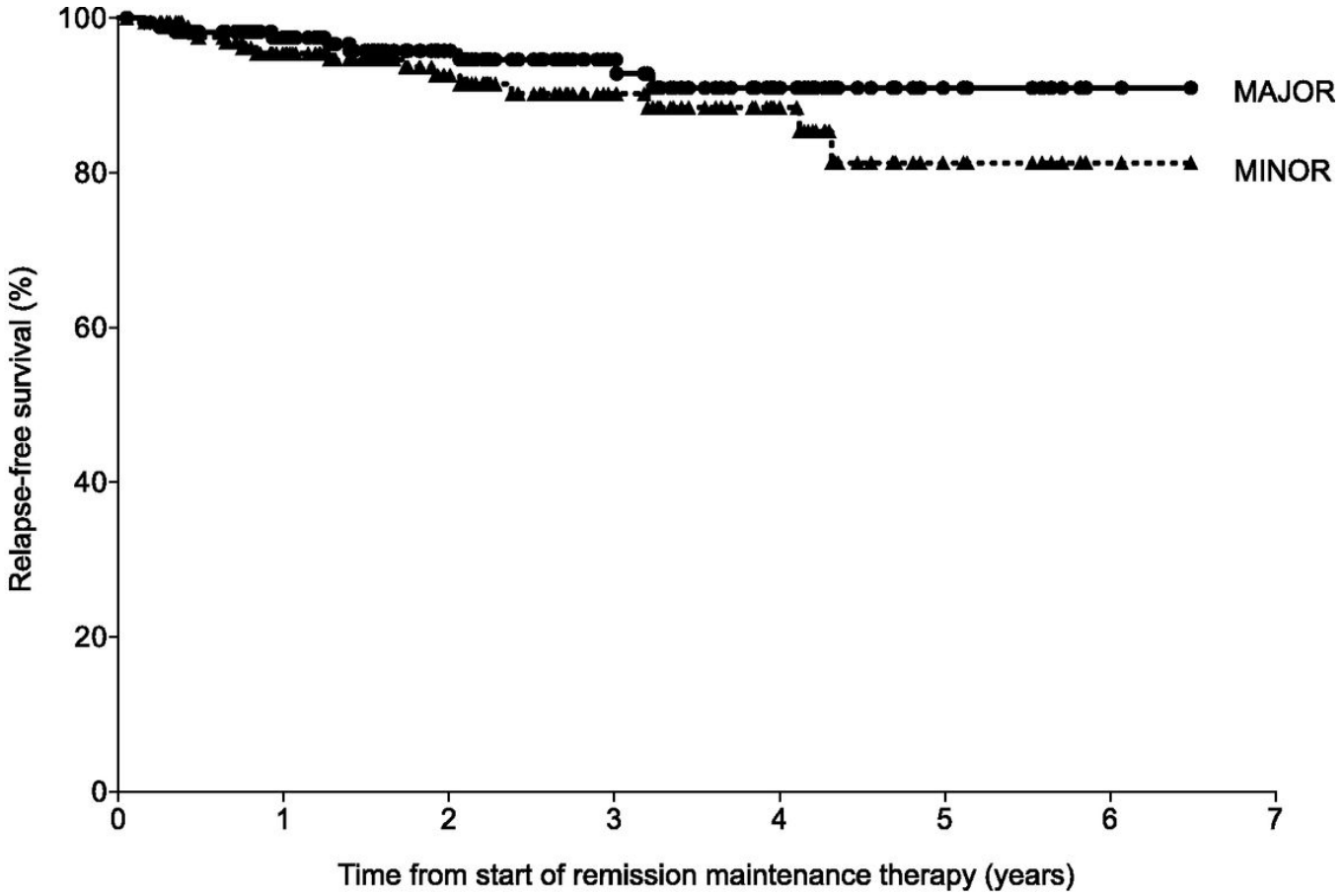
Arthritis Rheum. 2012 Nov;64(11):3770–3778

Long-Term Maintenance Therapy Using Rituximab-Induced Continuous B-Cell Depletion in Patients with ANCA Vasculitis

William F. Pendergraft III,[*†‡] Frank B. Cortazar,[§] Julia Wenger,[†] Andrew P. Murphy,[†‡] Eugene P. Rhee,[†] Karen A. Laliberte,[†‡] and John L. Niles[†‡]*

- a single center retrospective analysis involving 172 patients (mean age=60years, 57% myeloperoxidase–ANCA) treated from April of 2006 to March of 2013
- maintenance therapy using rituximab to induce complete and continuous B-cell depletion for up to 7 years
- most patients received 1000 mg rituximab every 4 months

Minor and major relapse-free survival of ANCA vasculitis patients undergoing continuous B-cell depletion.



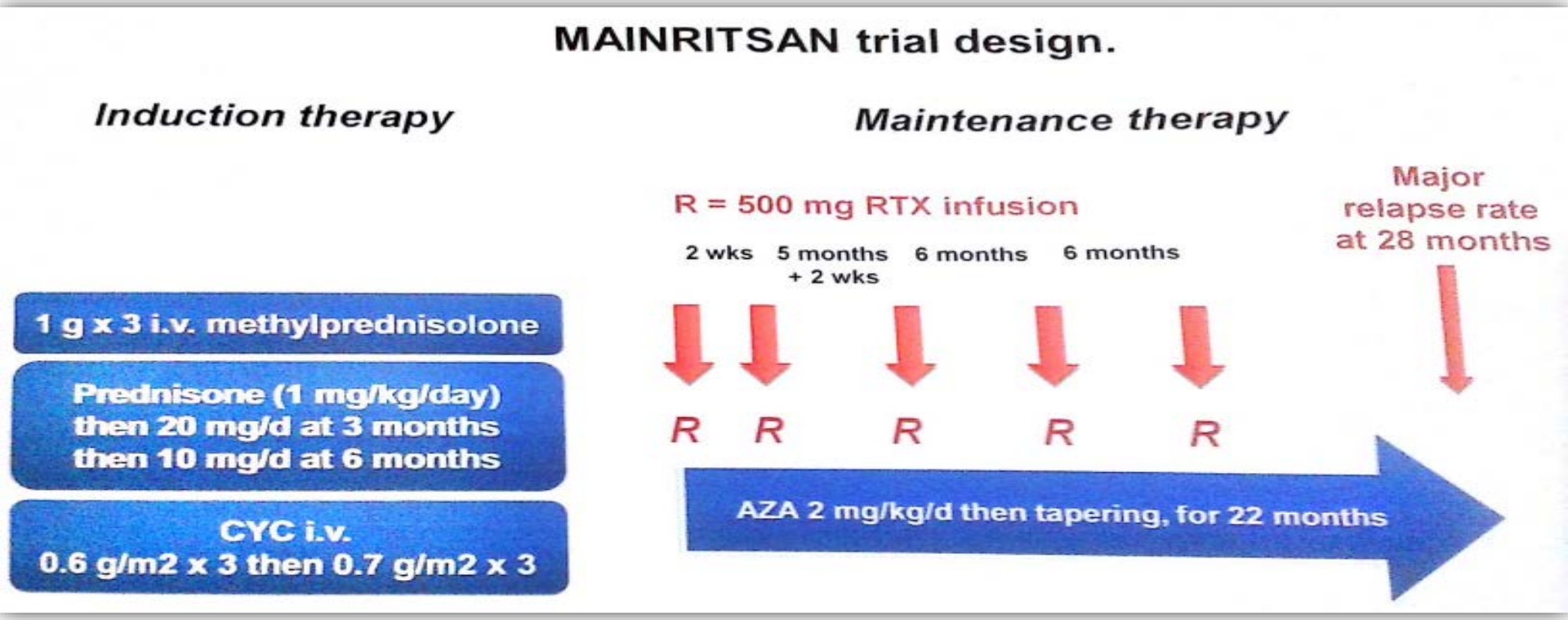
Number at risk

Major relapse	172	131	86	55	32	11	3
Minor relapse	172	111	67	42	24	9	3

William F. Pendergraft III et al. CJASN 2014;9:736-744

CJASN

Rituximab nella terapia di mantenimento delle AAV



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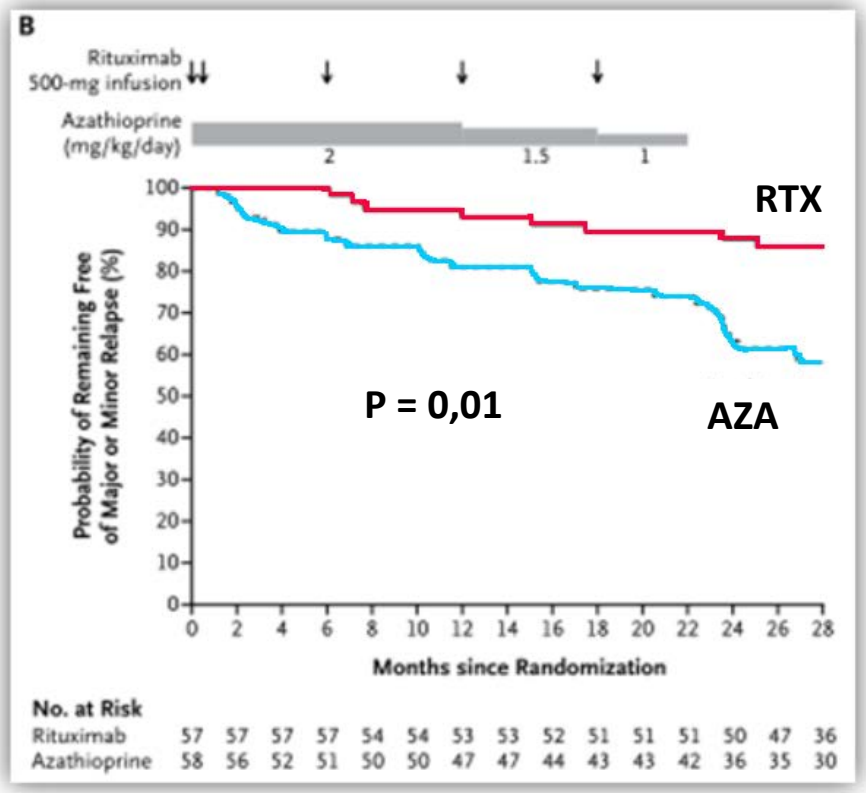
Rituximab versus Azathioprine for Maintenance in ANCA-Associated Vasculitis

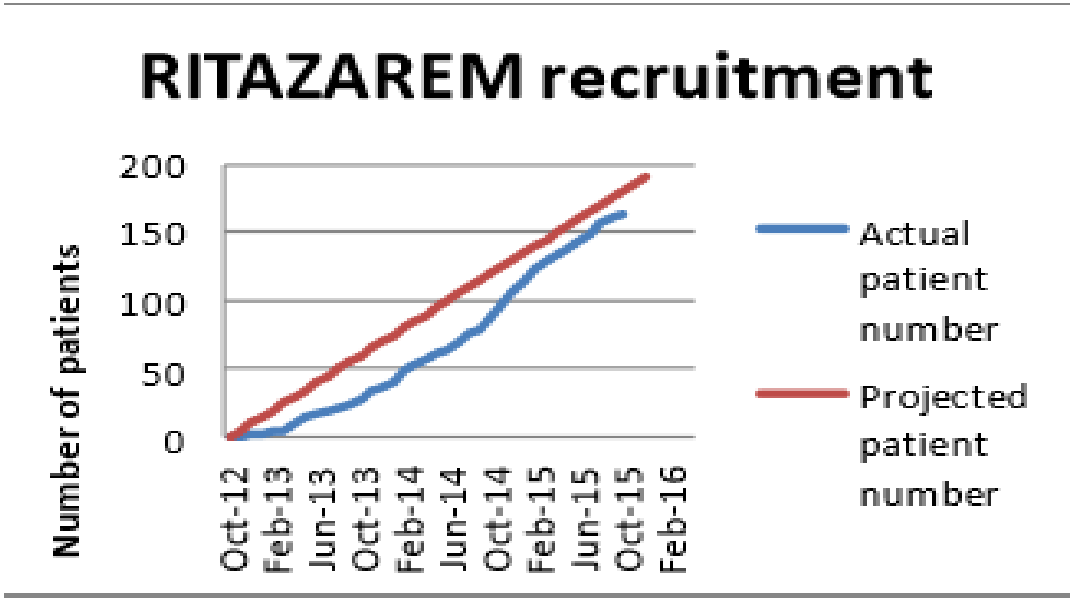


Hazard ratio for major or minor relapse in patients in the azathioprine group as compared with Rituximab recipients was 3,53 (95% CI, 1,49 to 8,40; P = 0,01)

Guillevin L et al, N Engl J Med 2014; 371: 1771-80

RITAZAREM: AN INTERNATIONAL, OPEN LABEL, RANDOMISED CONTROLLED TRIAL COMPARING RITUXIMAB WITH AZATHIOPRINE AS MAINTENANCE THERAPY IN RELAPSING ANCA ASSOCIATED VASCULITIS

- 1:1, parallel, open randomized trial evaluating the efficacy of rituximab or azathioprine maintenance therapy in relapsing AAV.
- 190 patients with relapsing AAV will be enrolled across Europe, North America, and Australasia
- **Induction therapy:**rituximab (4 x 375mg/m^2), and glucocorticoid,.
- **Maintenance therapy**: at month 4 those with stable disease pts will be randomised to receive
  repeat rituximab (1g at 4, 8, 12, 16, 20 months)
  or azathioprine (2mg/kg/day)
  stopping at month 27)
- All patients will receive glucocorticoids (standardized taper) concomitant with their allotted maintenance regimen



Comparison Study of Two Rituximab Regimens in the Remission of ANCA Associated Vasculitis (MAINRITSAN 2)

Experimental: Rituximab infusion according biological parameters Rituximab infusion based on ANCA and CD19 lymphocytes	**Drug: Rituximab (Arm B) Rituximab infusion will be performed at D1 then ANCA status and CD19+ lymphocyte count will be monitored every 3 months, and patients will receive new 500 mg rituximab infusions either if CD19 are > to 0/mm3, or if ANCA are positive again or if ANCA titer significantly raises. All patients received corticosteroids, starting from induction with prednisone (or equivalent) at a dose of 1 mg/kg/day with gradual tapering according to a regimen adjusted to body weight over a mean of 18 months since diagnosis**
Active Comparator: **Systematic** rituximab infusion Semestrial rituximab infusion **until 18 months**	Rituximab infusion will be performed at D1, D15, M6, M12 and M18 (i.e. a total of 5 infusions), at the dose of 500 mg at a fixed dosage.All patients **received corticosteroids**, starting from induction with prednisone (or equivalent) at a dose of 1 mg/kg/day with gradual tapering according to a regimen adjusted to body weight **over a mean of 18 months since diagnosis.**

Conclusioni

Rituximab **come 1° scelta**
nella terapia di induzione della remissione

- pazienti “fragili” (anziani o con comorbidità)
- pazienti giovani (in difesa della loro fertilità)
- nelle forme di malattia”granulomatosa” localizzata
- nella malattia alla recidiva

Conclusioni

Rituximab **come 1° scelta**
nella **terapia di mantenimento della remissione***

- nei pazienti con GPA **dalla** 1°recidiva
- nelle forme di **malattia"granulomatosa" localizzata** "resistenti" es pseudotumore orbitario, stenosi sottoglottiche o tracheo-bronchiali
- nei pazienti con scarsa compliance alla terapia

***schema proposto dai francesi : 4 somminstrazioni da 500 mg ogni 6 mesi