Treatment of Primary Vasculitis

Outlines

I. Introduction
II. Conventional Treatments
III. Promising Biologics

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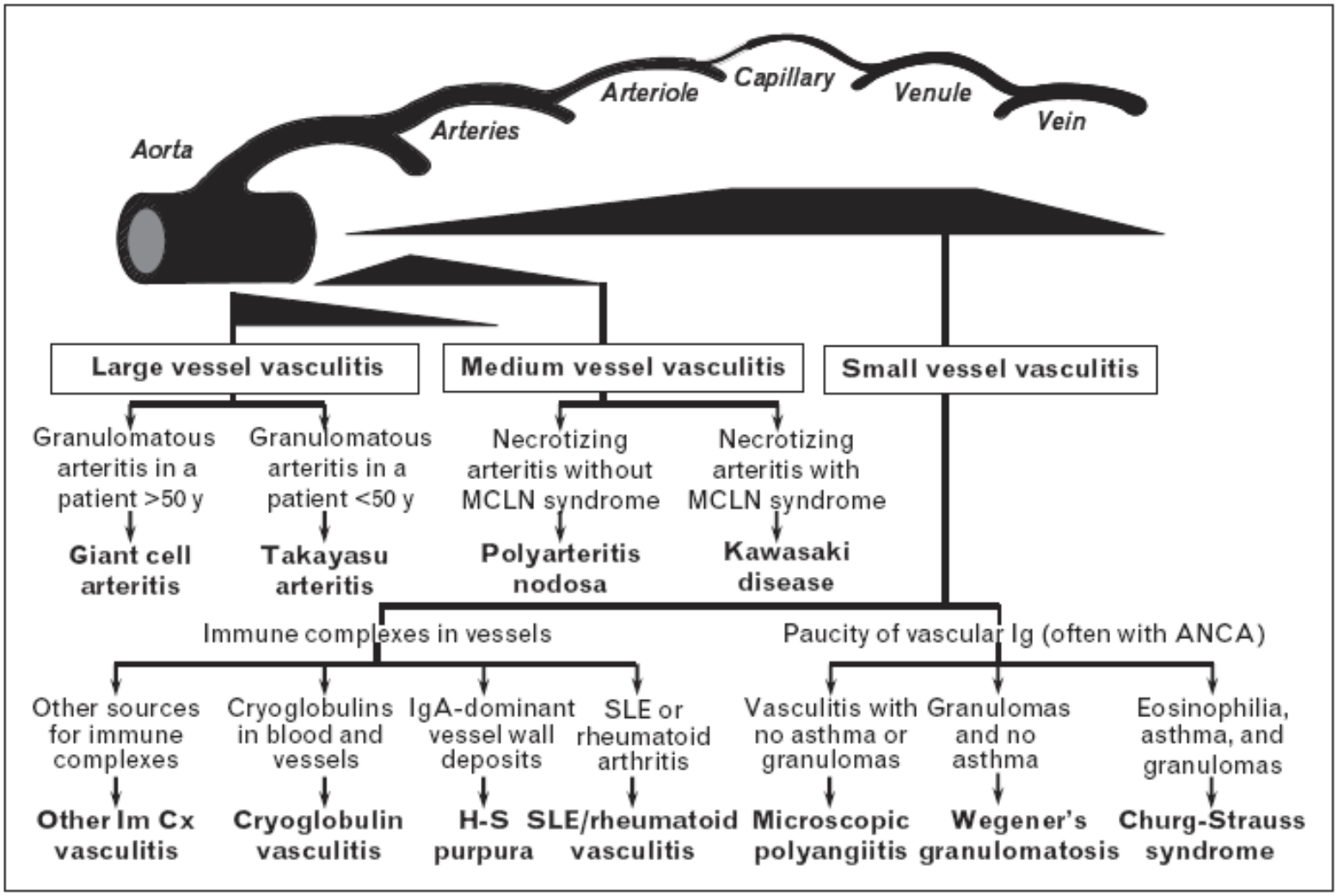
Figure 1 Diagram depicting the predominant vascular distributions of major forms of primary systemic vasculitis



Algorithm showing some of the pathologic and clinical features that allow classification and diagnostic differentiation among the different forms of vasculitis. ANCA, antineutrophil cytoplasm autoantibody; H-S purpura, Henoch-Schönlein purpura; Im Cx, immune complex; MCLN syndrome, mucocutaneous lymph node syndrome; SLE, systemic lupus erythematosus.

Principles of Treatment for Vasculitis (I)

- **A wide spectrum of diseases with varying degrees of severity**
  - **Look for offending antigen and remove it**
  - **Look for underlying disease and treat it**
- **Risk-versus-benefit ratio of any therapeutic approach carefully weighed**
  - **Potential side effect may be substantial**
  - **Disease severity**
    - **Wegener's graulomatosis vs Idiopathic cutaneous vasculitis**

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Principles of Treatment for Vasculitis (II)

- **Physician should be thoroughly aware of toxic side effects of therapeutic agents employed**
- **TMP-SMX recommended as prophylaxis against *P. jiroveci* infrction**
- **Each patient is unique and require individual decision-making**

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A common error

- is treating patients with high doses of immunosuppressive agents **for too long**. The most appropriate use of medication such as cyclophosphamide and corticosteroids is to induce remission as quickly as possible with early, aggressive treatment regimens and then to convert patients to safer treatments for maintenance of remission

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ANCA-positive Small Vessel Vasculitis causing Pulmonary-Renal Syndrome

Wegener's Granulomatosis

Churg-Strauss disease

Microscopic polyangitiis

Conventional Treatment for ANCA-Associated Vasculitis

- **The era before steroid**
  - **High mortality: mean survival of 5 months in WG**
- **Steroid use in 1960's**
  - **5-year survival rate: improved from 10% to 50%**
- **Glucocorticoid plus cyclophosphamide**
  - **Standard therapy**
  - **Proposed first by Anthony S. Fauci in 1973, and popularized after 1978**
  - **5-year survival rate: 80%**

(Fauci A, et al. N Engl J Med 1979;301:235-8)

Outcome of Conventional Treatment of ANCA-Associated Primary Systemic Vasculitis

	Wegener's granulomatosis[1]	Churg-Strauss syndrome[2]	Microscopic polyangiitis[3]
Remission rate	93%	81-92%	>90%
Survival rate	87% (6 months-24 years)[4]	96.9%	74% (5-year)
Relapse rate	50%	26-38%	25%

- 1. Annals of Internal Medicine. 1983; 98: 76-85.
- 2. Lancet 2003; 361: 587-94.
- 3. Arthritis & Rheumatism 1999; 3: 421-430.
- 4. Rheumatology 2nd Edition. Volume Two. Section 6-8. Ch. 22.

Adverse Effects of Conventional Treatment

Cyclophosphamide

- **NIH experience:**
  - **permanent damage in over 50% WG**
  - **1.1 episode per patient; 26%: severe or life-threatening**
  - **Malignancy: bladder ca.(33 x), lymphoma(11.1x)**
  - **Infections: *Pneumocystitis carinii* (PCP) infection (20%)**
  - **Gonadal failure**

Klippel JH, et al. Rheumatology 2nd Edition. Volume Two. Ch.22. Mosby. 1998

Adverse Effects of Conventional Treatment

- **Glucocorticoid**
  - Osteoporosis
  - Hypertension
  - Hyperglycemia
  - Dyslipidemia
  - Muscle weakness and fatigability
  - Cutaneous striae
  - Easy bruisability
  - Buffalo hump and moon face
  - Infection

Alternative Strategies to Reduce the Toxic Effects of Cyclophosphamide

Therapeutic Approach or Strategy	Examples
Use of less toxic agents in maintenance therapy	Azathioprine; Methotrexate; Mycophenolate mofetil
Noncyclophosphamide treatment options	Steroid with methotrexate for the induction of remission of nonsevere disease

Langford. C.A. N Engl J Med. 349: 3-4, 2003. **Perspective**

Treatment for ANCA-positive Systemic Vasculitis

- **Cyclophosphamide induction for severe disease**
  - **Oral daily cyclophosphamide 2 mg/kg plus prednisone 1mg/kg**
  - **Complete remission 75%**
- **MTX induction for nonsevere disease**
- **Remission maintenance**
  - **MTX 20-25mg/week**
  - **Azathioprine 2mg/kg**
  - **Relapse 50%**

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Azathioprine or Methotrexate Maintenance for ANCA-Associated Vasculitis

Christian Pagnoux, M.D., M.P.H., Alfred Mahr, M.D., Ph.D., Mohamed A. Hamidou, M.D., Jean-Jacques Boffa, M.D., Marc Ruivard, M.D., Jean-Pierre Ducroix, M.D., Xavier Kyndt, M.D., François Lifermann, M.D., Thomas Papo, M.D., Marc Lambert, M.D., Ph.D., José Le Noach, M.D., Mehdi Khellaf, M.D., Dominique Merrien, M.D., Xavier Puéchal, M.D., Ph.D., Stéphane Vinzio, M.D., Pascal Cohen, M.D., Luc Mouthon, M.D., Ph.D., Jean-François Cordier, M.D., and Loïc Guillevin, M.D., for the French Vasculitis Study Group*

RESULTS

Among 159 eligible patients, 126 (79%) had a remission, were randomly assigned to receive a study drug in two groups of 63 patients each, and were followed for a mean (±SD) period of 29±13 months. Adverse events occurred in 29 azathioprine recipients and 35 methotrexate recipients (P=0.29); grade 3 or 4 events occurred in 5 patients in the azathioprine group and 11 patients in the methotrexate group (P=0.11). The primary end point was reached in 7 patients who received azathioprine as compared with 12 patients who received methotrexate (P=0.21), with a corresponding hazard ratio for methotrexate of 1.65 (95% confidence interval, 0.65 to 4.18; P=0.29). There was one death in the methotrexate group. Twenty-three patients who received azathioprine and 21 patients who received methotrexate had a relapse (P=0.71); 73% of these patients had a relapse after discontinuation of the study drug.

CONCLUSIONS

These results do not support the primary hypothesis that methotrexate is safer than azathioprine. The two agents appear to be similar alternatives for maintenance therapy in patients with Wegener's granulomatosis and microscopic polyangiitis after initial remission. (ClinicalTrials.gov number, NCT00349674.)

Treatment for Polyarteritis Nodosa

- **Cyclophosphamide plus prednisone**
- **Glucocorticod alone in less severe cases**
- **HBV-related cases**
  - **Favorable results with antiviral therapy + glucocorticoid + plasma exchange**
- **Relapse in only 10%**

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Treatment for Giant Cell Arteritis

- **Disease-related mortality is very uncommon**
  - **Cause of death: CVA, AMI or aortic aneurysm rupture**
- **Goals are to reduce symptoms and prevent visual loss**
- **Prednisone 40-60 mg/d for 1 month, followed by a gradual tapering**
  - **ESR as a useful indicator of disease activity**
- **Aspirin reduce cranial ischemic complication**

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Treatment for Takayasu's Arteritis

- **Long-term outcome varied widely with 5 year mortality ranged from 0-35%**
  - **Disease related mortality:CHF, CVA, AMI, aneurysm rupture or renal failure**
- **Prednisone 40-60mg/d alleviates symptoms but increased survival ?**
- **Aggressive surgery and/or angioplastic approach to stenosed vessels markedly improve outcome**
- **Surgical correction undertaken only when vascular inflammation well controlled**
- **MTX in refractory or steroid –dependent case**

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Treatment for Kawasaki Disease

- **Generally benign and self-limited**
- **25% associated with coronary artery aneurysm with overall fatality rate of 0.5-2.8%**
- **Reduce the prevalence of coronary artery abnormalities when administrated early**
  - **High dose IV γ globulin (2g/kg as a single infusion over 10 h) plus**
  - **Aspirin (100mg/kg for 14 days followed by 3-5 mg/kg for several weeks)**

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Treatment for Behcet's syndrome

- **The severity usually abates with time**
- **Life expectancy without CNS and major vessel disease seems to be normal and only serious complication is blindness**
- **Mucous membrane involvement**
  - **Topical glucocorticoid**
  - **Thalidomide (100mg/day) in severe cases**
  - **Colchicine can be beneficial**
  - **Aspirin for thrombophlebitis**
- **Uveitis and CNS involvement**
  - **Prednisone 1mg/kg/day + azathioprine 2-3 mg/kg**
  - **Interferon-α**

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Treatment for Henoch-Schonlein Purpura

- **Prognosis is excellent.**
  - **Mortality is exceedingly rare.**
  - **1-5% of children progress to end-stage renal disease**
- **Most recover completely. Some do not require therapy**
- **Prednisone 1mg/kg/day, tapered according to clinical response**
  - **Not proven beneficial in skin or renal disease**
  - **RPGN…plasma exchange + cytotoxic drugs**
- **Disease recurrences 10-40%**

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Treatment for Essential Mixed Cryoglobulinemia

- **Acute mortality is uncommon**
- **The presence of glomerulonephritis is a poor prognostic sign**
  - **15% progress to end-stage renal disease with 40%later experiencing fatal CVD, infection or liver failure**
- **IFN-α and ribavirin in HCV-related cases**
  - **Clinical improvement depend on virologic response**
- **Complete response to steroid in only 7%**
- **Plasma exchange plus cytotoxic agents**
  - **Anecdotal reports**
  - **Carry significant risks**

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Treatment for Idiopathic Cutaneous Vasculitis

- **Remove the precipitating factor if recognized**
- **Treat the underlying disease**
- **No therapy needed if apparently self-limited**
- **For persistent vasculitis**
  - **Weigh the balance between the degree of symptoms and the risk of treatment**
  - **In general, treatment has not been satisfactory**
  - **Glucocorticoid 1mg/kg/day with rapid tapering where possible**
  - **Steroid-refractory**
    - **MTX, azathioprine, dapsone, colchicine, NSAID**
    - **Cyclophosphamide never be used because of potential toxicity**

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Prognosis of Vasculitis

Determined largely by the following four questions:

1. **Was the diagnosis established before the occurrence of major, irreversible organ damage?**
2. **Was aggressive (but appropriately dosed) treatment begun in a timely fashion?**
3. **Was there careful monitoring during treatment, and were specific steps taken to avoid drug-induced toxicity**
4. **Were the potentially toxic medications that induced remission stopped at an appropriate juncture and substituted for less dangerous medications (or simply stopped altogether)**

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Promising Biologics for Primary Vasculitis

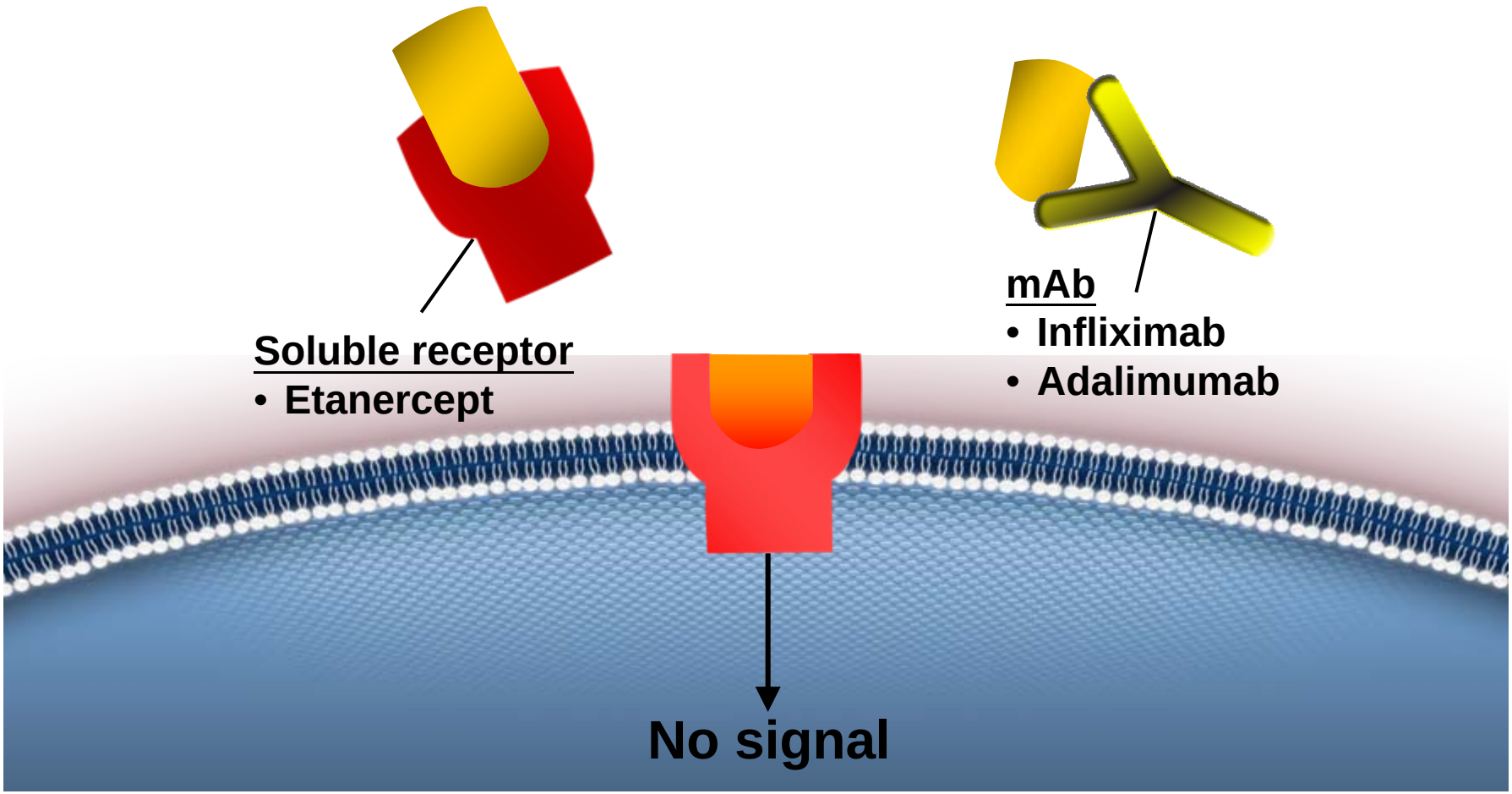
- **Anti-cytokine (TNF-α blockers)**
- **B cell depletion (Anti-CD20 mAb)**

TNF-α blockers

- **Soluble TNF-α receptor**
  - **Etanercept (Ebrel)***
    - **Subcutaneous injection of 25 mg twice weekly**
- **Monoclonal antibody**
  - **Infliximab (Remicade)**
    - **3mg/kg, at weeks 0, 2, 6, and 8 and every 8 weeks thereafter**
  - **Adalimumab (Humira)***
    - **Subcutaneous injection of 40 mg every 2 weeks**

* available in Taiwan

TNF Inhibitors



Clinical Trials of TNF-α Blockers in Primary vasculitis

Promising in

Takayasu's arteritis: Etanercept and Infliximab
(Ann Rheum 2008; 67:1567-9)

Behct's disease: Infliximab (J Rheumatol 2004;31:1362)
Etanercept (J Rheumatol 2005;32:98)

Ineffective in

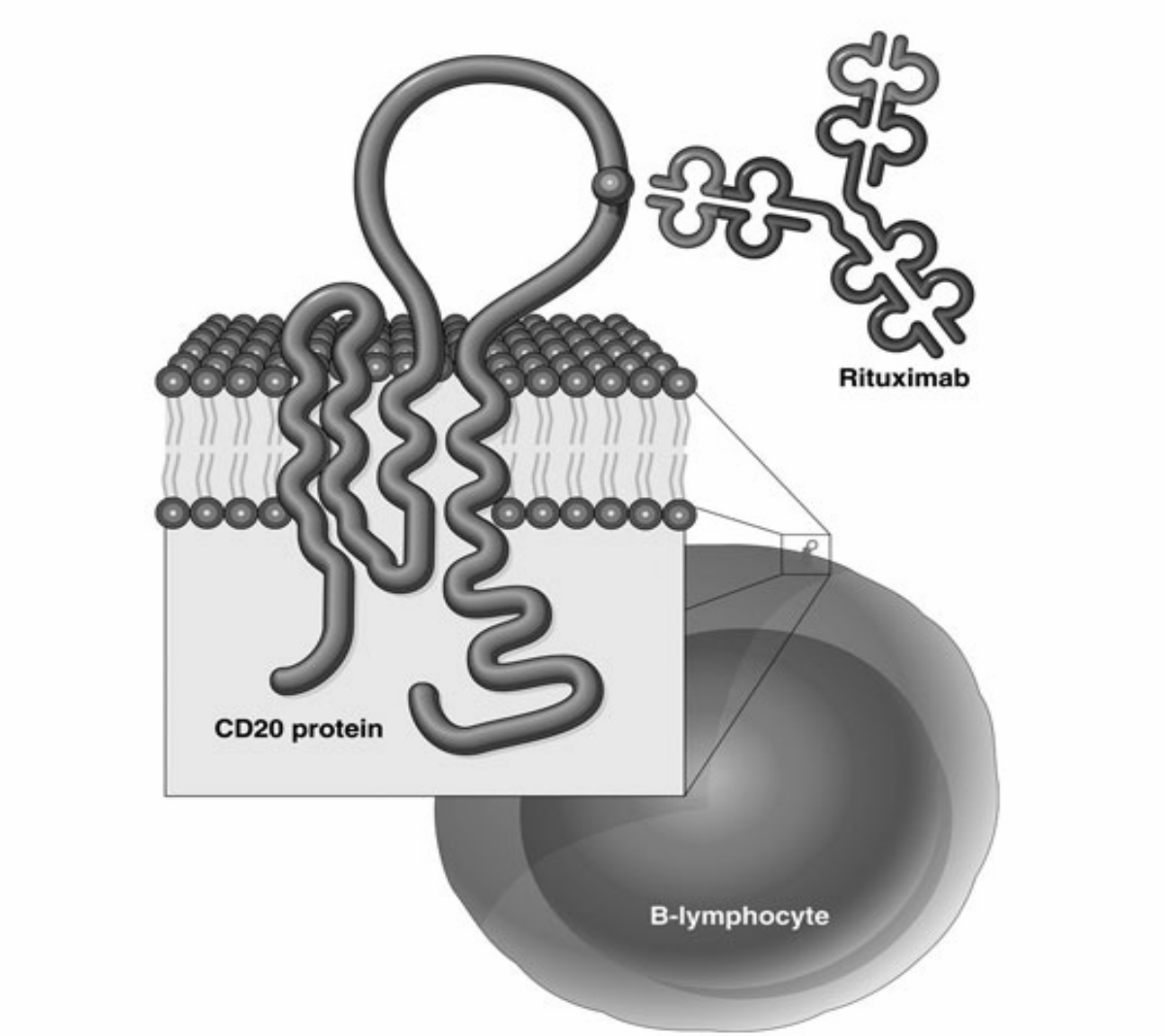
Giant cell arteritis: Infliximab
(Ann Intern Med 2007;146:621-30)

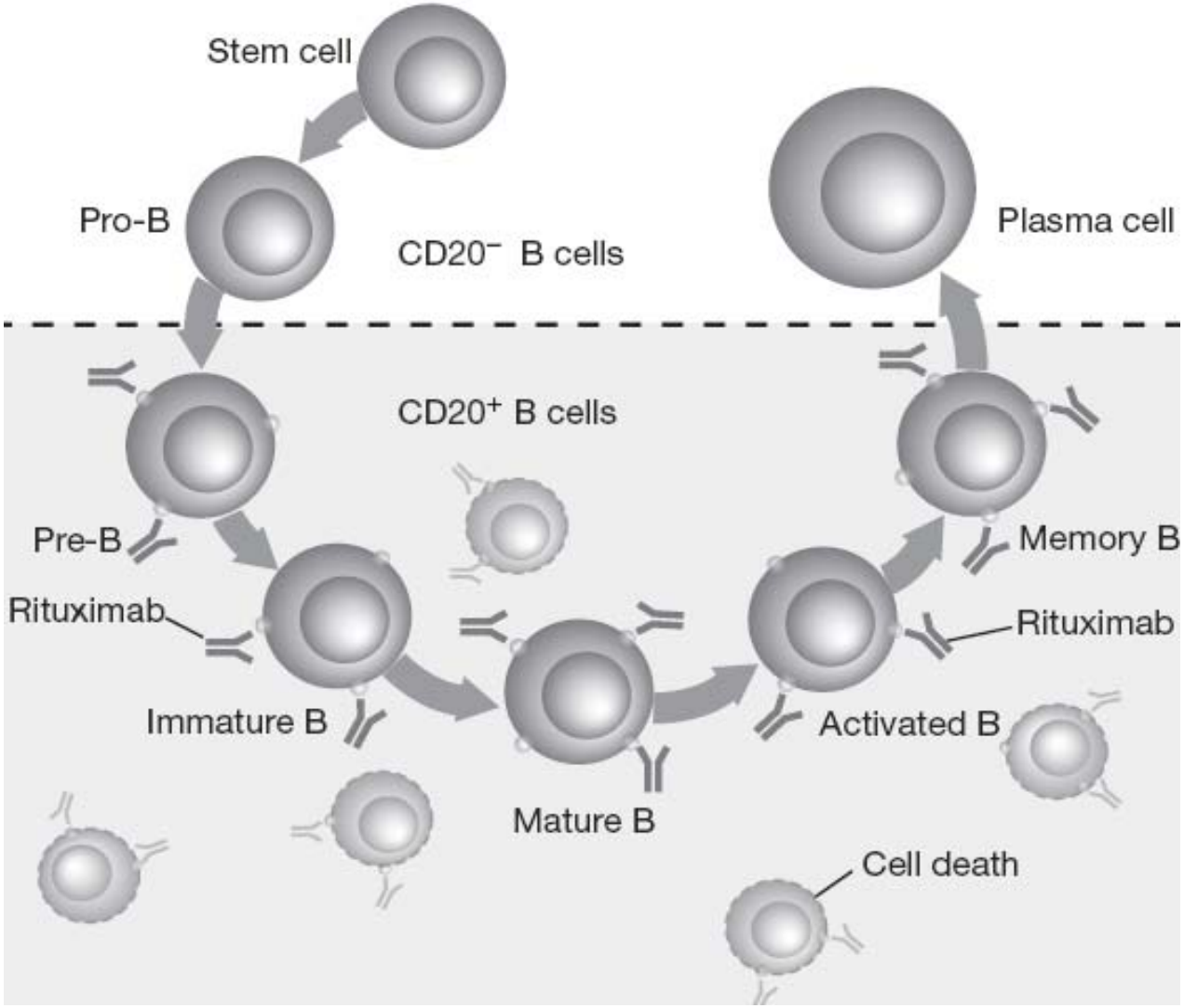
Wegener's granulomatosis:

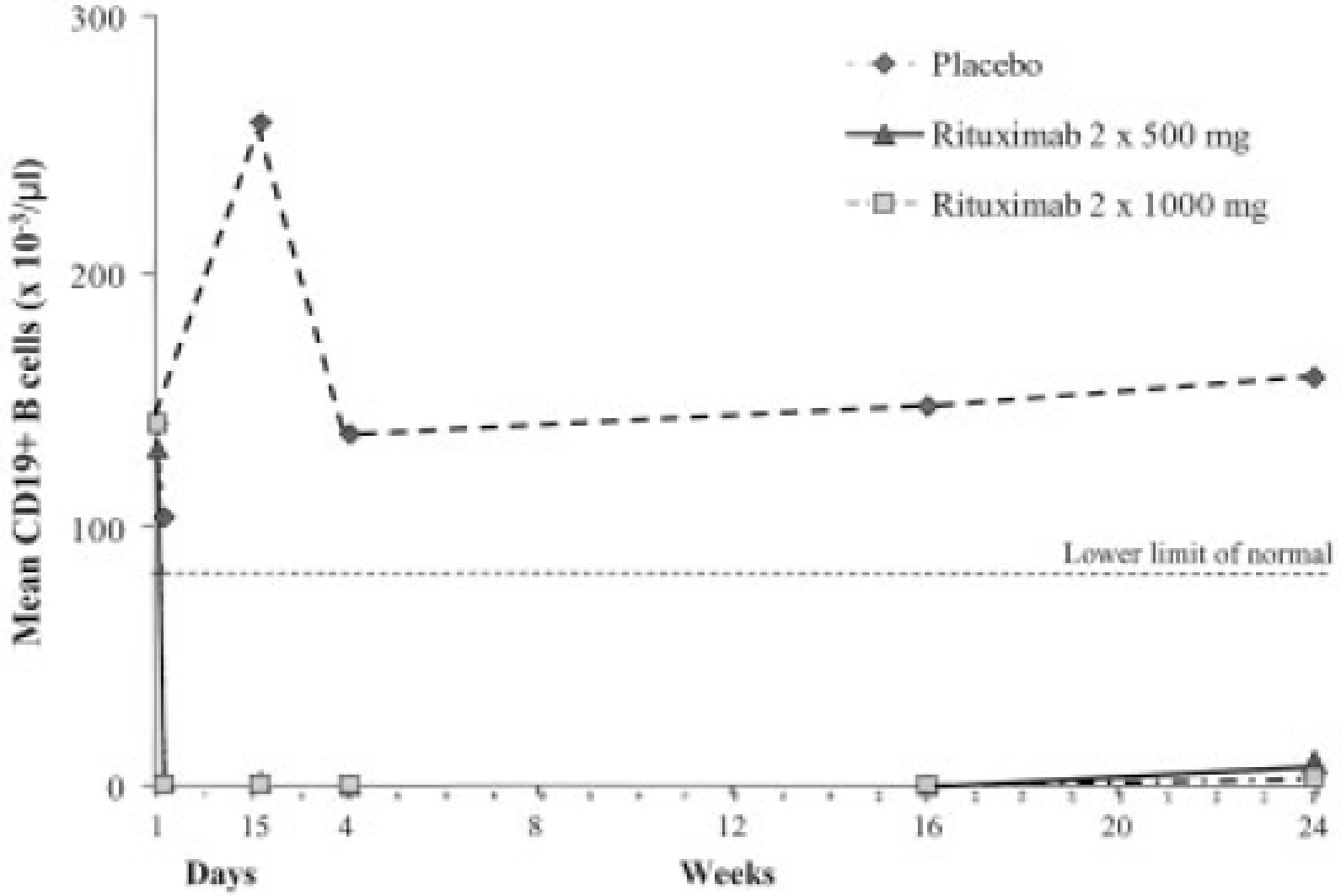
WGET: Eternacept…ineffective and increased rate of malignancy (SIR 3.12)
(N Engl J Med 2005;352:351-61)

Efficacy ?? In Infliximab or adalimumab

B cell depletion (Anti-CD20 MAb, Rituximab)




Stem cell
Pro-B
CD20⁻ B cells
Plasma cell
CD20⁺ B cells
Pre-B
Rituximab
Immature B
Mature B
Activated B
Memory B
Rituximab
Cell death


Placebo
Rituximab 2 x 500 mg
Rituximab 2 x 1000 mg
Mean CD19+ B cells (x 10-3/µl)
300
200
100
0
Lower limit of normal
1
15
4
8
12
16
20
24
Days
Weeks

Clinical Trials of Rituximab in mixed cryoglobulinemic vasculitis

- Rituximab: partial or complete remission:
  (Review in Ann Rheum Dis 2008;67: 1431-6)
  - Skin involvement (80%); arthralgia (79%); neuropathy (93%); glomerulonephritis (83%)

- Rituximab combined with Peg-IFN-ribavirin
  (Ann Rheum Dis 2008;67: 283-7)
  - Open-label pilot study in 16 refractory HCV-MC vasculitis
  - Clearance of HCV RNA abd cryoglobulin load
    - Complete (62.5%); partial (31.2%)
  - **Clinical improvement**
    - Renal (57.2%); polyneuropathy (38.4%); purpura (84.6%); arthralgia (83.4%); leg ulcers (100%)

Clinical Trials of Rituximab in ANCA-associated vasculitis

- **For refractory or relapsing cases**
- **6 papers of case series in literature (2005-2008)**
  - **Total 44 cases: WG (41) and MPA (3)**
  - **Remission in 36 cases (81.8%)**
  - **Partial response in 5 cases (11.4%)**
  - **No response in 3 cases**

- **4 papers of prospective open-label trials (2006)**
  - **Total 39 cases: WG (31), MPA (7) and CSS (1)**
  - **Remission: 30 cases (76.9%)**
  - **Partial response: 3 cases (7.7%)**
  - **No response: 6 cases**

Curr Opin Rheumtol 2009;21:3-9

Summary

- **Systemic vasculitides are a diverse group of disorders with varied presentation, pathogenesis, vessel involvement, prognosis and therapeutic approach**
- **Cyclophosphamide plus steroids is the standard therapy for severe form of primary systemic vasculitis, esp. ANCA-associated vasculitis, but with substantial toxicities**
- **Biologic agents represent the next evolution in treatment for primary systemic vasculitis**

Thank you for your attention!