Latest trials on ANCA-related vasculitis

---2015-12， Hong Kong

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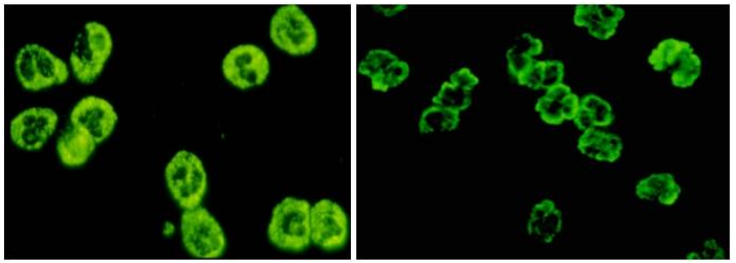
Outline

- **Characteristics of ANCA-related vasculitis in China**
- **Latest trials on ANCA-related vasculitis**

2012 Chapel Hill Consensus Conference Vasculitis Nomenclature



Large Vessel Vasculitis
- Giant Cell Arteritis
- Takayasu Arteritis

Medium Vessel Vasculitis
- Polyarteritis Nodosa
- Kawasaki Disease

Small Vessel Vasculitis
- ANCA-Associated Vasculitis
  - Microscopic Polyangiitis-----**MPA**
  - Granulomatosis with Polyangiitis (Wegener's)-----**GPA**
  - Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss)-**EGPA**
- Immune Complex Vasculitis
  - Anti-GBM Disease
  - IgA Vasculitis (Henoch-Schönlein)
  - Cryoglobulinemic Vasculitis
  - Hypocomplementemic Urticarial Vasculitis (Anti-C1q Vasculitis)

Variable Vessel Vasculitis (Cogan's, Behcet's, etc.)

Single Organ Vasculitis (cutaneous SVV, primary CNS vasculitis, etc.)

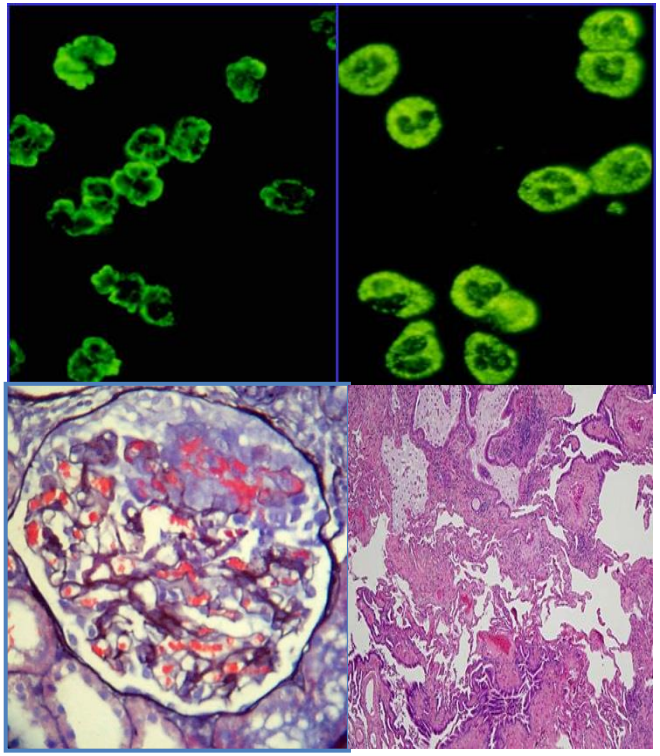
Vasculitis Associated with Systemic Diseases (e.g. Rheumatoid, Lupus, Sarcoid, etc.)

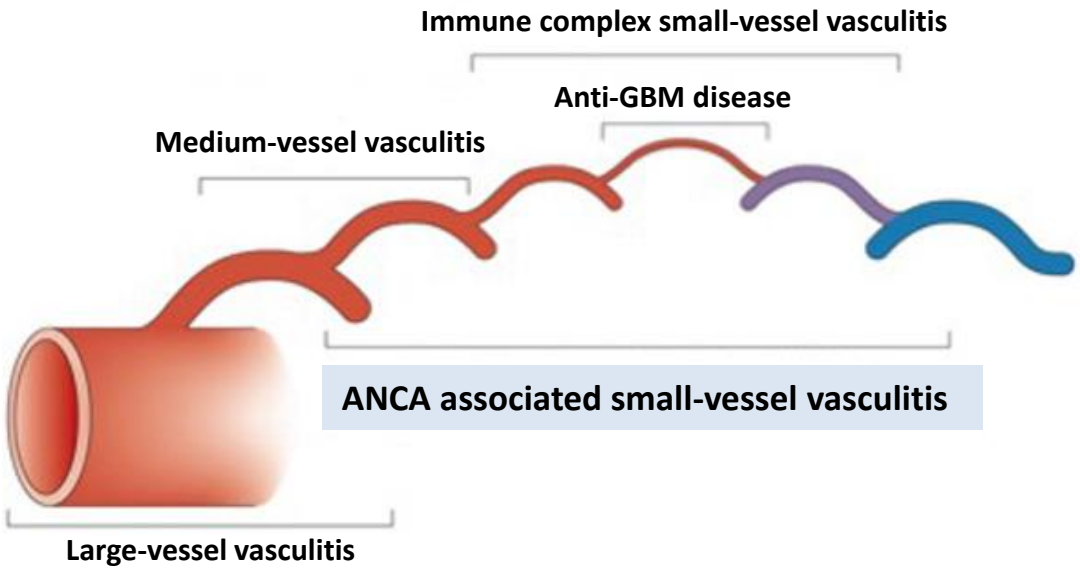
Vasculitis Associated with Probable Etiologies (e.g. HBV, HCV, drug, cancer, etc.)

Arthritis Rheum 2012; 65: 1–11

ANCA Associated Vasculitis (AAV)

- **Anti-Neutrophil Cytoplasmic Autoantibodies (ANCA)**
  - **The two primary antigenic targets**
    - **Myeloperoxidase (MPO)**
    - **Proteinase 3 (PR3)**



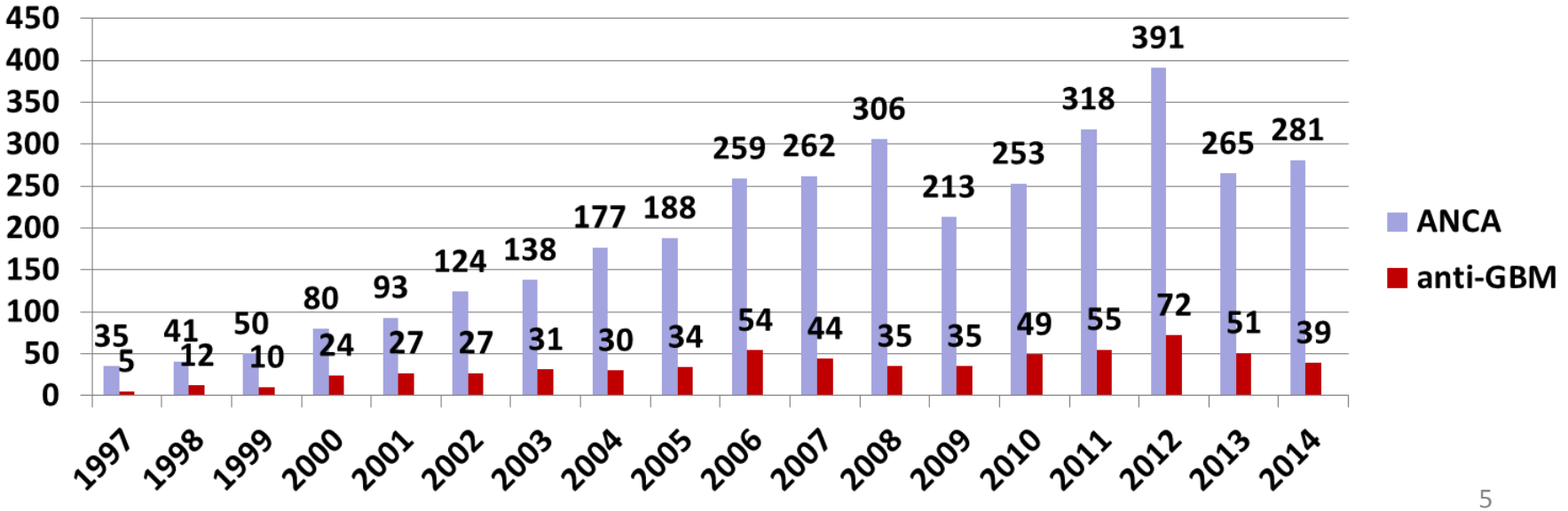


Jennette JC & Falk RJ, Nat Rev Rheumatol. 2014

ANCA disease in China

- **Incidence in China: unclear**
  - **1980s: unawareness**
  - **1508 cases diagnosed in our referral diagnostic center within 5 years**

ANCA disease is not rare in Chinese



Disease spectrum and ANCA antigen

- **Disease spectrum**
  - **GPA: 87/426（20.4%）**
  - **MPA: 337/426 （79.1%）**
  - **EGPA: 2/426 （0.5%）**

- **Target antigens of ANCA**
  - **MPO:PR3=213:32（6.7:1)**
  - **Elderly: MPO:PR3=19:1**

- **MPO-ANCA is predominant in Chinese patients with AAV**
- **Renal Involvement is common and sever**

- **GPA(WG): 89 cases（ACR＋CHCC）**
  - **pANCA/MPO: 54/ 89 (60.7%)**

Chen M, et al. *Postgrad Med J* 2005;81:723-727
Chen M, et al. *Kidney Int* 2005;68:2225-2229
Chen M, et al. *Medicine* 2008;87(4):203-209
Li ZY, et al. *Arthritis Rheumatol*. 2014 Jul;66(7):1920-6.

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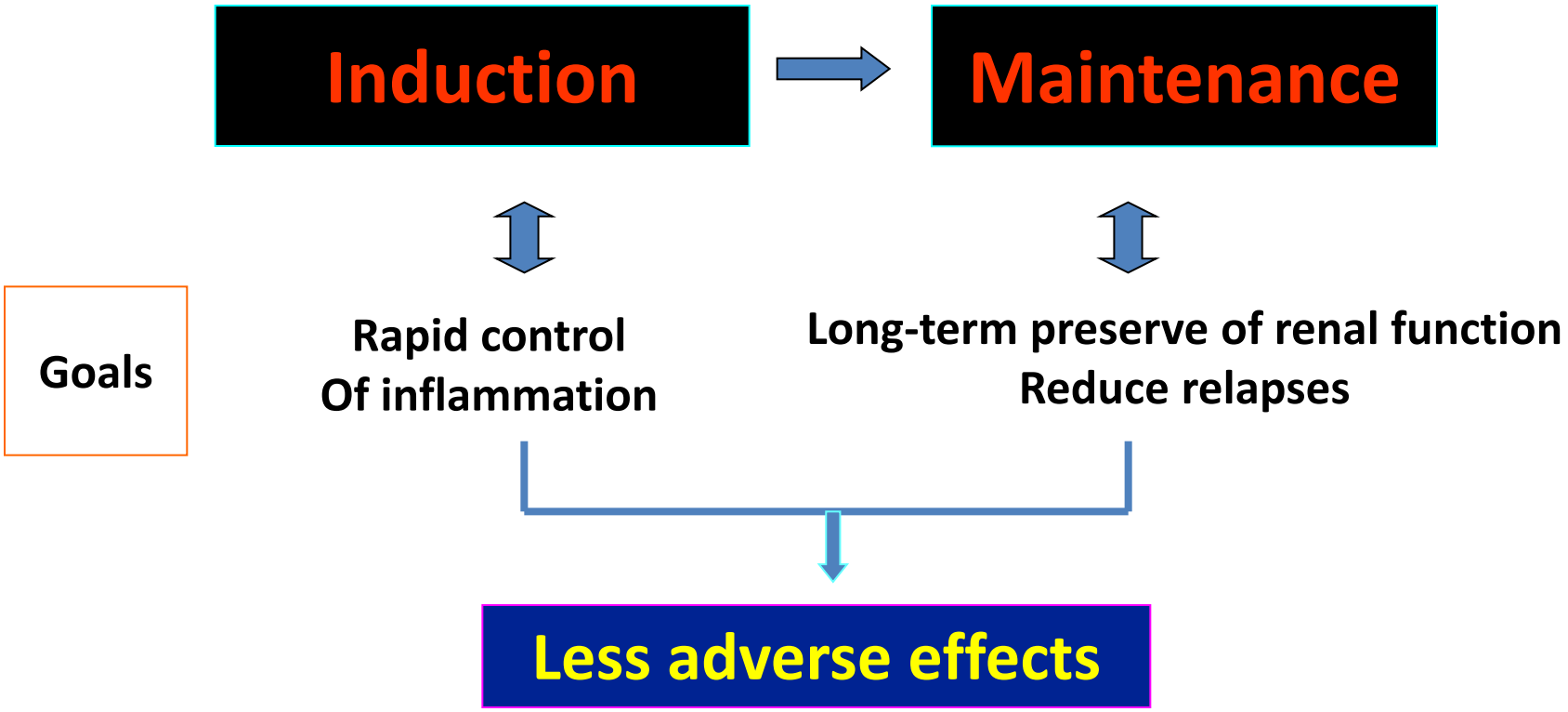
Treatment Strategy of AAV



KDIGO Guideline---Initial treatment (1)

- **We recommend that CTX and corticosteroids be used as initial treatment. (1A)**

- **We recommend that rituximab and corticosteroids be used as an alternative initial treatment in patients without severe disease or in whom CTX is contraindicated.(1B)**

KDIGO Guideline---Initial treatment (2)

- **Special patient populations**
  - **We recommend the addition of plasmapheresis for patients requiring dialysis or with rapidly increasing SCr. (1C)**
  - **We suggest the addition of plasmapheresis for patients with diffuse pulmonary hemorrhage.(2C)**
  - **We suggest the addition of plasmapheresis for patients with overlap syndrome of ANCA vasculitis and anti-GBM GN. (2D)**
  - **We suggest discontinuing CTX after 3 months in patients who remain dialysis-dependent and who do not have any extrarenal manifestations of disease.(2C)**

EUVAS approach to trials in AAV

- Subgroup according to severity
- High intensity treatment to induce remission, low intensity to prevent relapse
- Agree standard regimen by consensus
- Test against best alternative by randomised controlled trial
- Use standardised scoring systems (BVAS)

Induction trials

Name	Design	End point	Result
NORAM *(EUVAS) AR 2005*	MTX v oral CYC	Remission 6 months	MTX noninferior to CYC
CYCLOPS *(EUVAS) AIM 2009*	iv CYC v oral CYC	Time to remission	iv CYC noninferior to oral CYC
MEPEX *(EUVAS) JASN 2007*	PE v iv MP pulse	Dialysis independent 3 months	Renal survival better with PE than iv MP pulse
RITUXVAS *(EUVAS) NEJM 2010*	RTX + iv CYC x 2 v iv CYC	Sustained remission 12 months	RTX noninferior to CYC
RAVE *NEJM 2013*	RTX v oral CYC	Remission without pred 6 months	RTX noninferior to CYC

EUVAS-CYCLOPS study

- **149 patients**
  - **iv CTX: 15mg/kg/2 to 3 wks, (n=76)**
  - **daily oral CTX: 2mg/kg/d, (n=73)**
  - **Corticosteroids were used in both groups**
- **Remission rates at 9th month: similar**
- **iv CTX vs. oral CTX:**
  - **a lower cumulative dose of CTX**
  - **fewer episodes of leukocytopenia**
  - **more relapse**

Oral CTX may still be considered in patients with frequent relapses

Ann Intern Med. 2009; 150, 670-80

EUVAS--MEPEX study

- PE vs. MP pulse in AAV with severe ARF
- 137 patients with AAV-ARF (Scr>500μmol/L)
  - PE: 4L ×7 (n = 70)
  - MP: 1g ×3 (n=67).
- Both groups received standard pred + CTX.

Jayne DR, et al. J Am Soc Nephrol 2007; 18: 2180-8

- **End of 3 months: rate of dialysis-independence:**
  - **33 (49%) in MP vs. 48 (69%) in PE (95% CI 18-35%; P=0.02)**
- **End of one year: rate of ESRD**
  - **43% in MP vs 19% in PE (95% CI 6.1-41%).**
- **Mortality rate and SAE were comparable**

For pts with severe ARF, PE is superior to MP for renal recovery

Jayne DR, et al. J Am Soc Nephrol 2007; 18: 2180-8

Rituximab—RAVE study

- Chimeric monoclonal antibody directed to CD20
- RAVE study: rituximab vs. oral CTX in induction therapy (n=197)
  - Rituximab: 375 mg/m^2/w × 4
  - CTX: 2mg/kg/d
  - Corticosteroids were used in both groups

Rituximab was not inferior to CTX in induction therapy

Stone, J. H. et al. N Engl J Med. 2010; 363: 221–232

Induction trials in progress

Name	Design	End point
MYCYC *(EUVAS) completed in 2011*	**MMF v iv CYC**	**Remission at 6 months**
PEXIVAS *(EUVAS) Start 2010*	**PLEX + CYC or RTX v CYC or RTX (high or low dose pred)**	**Composite of all-cause mortality and ESRD**
CLEAR	**CCX168 (C5aR inhibitor) + CYC v pred + CYC**	**Safety/efficacy of CCX168**
SPARROW	**Gusperimus (CNI) v CYC + MTX or AZA**	**Proportion patients in complete or partial remission**
ALEVIATE *(EUVAS)*	**Alemtuzumab (CD52) 60mg v 30 mg**	**Safety/efficacy of Alemtuzumab**

KDIGO Guideline---Maintenance therapy (1)

- **We recommend maintenance therapy in patients who have achieved remission. (1B)**

- **We suggest continuing maintenance therapy for at least 18 months in patients who remain in complete remission. (2D)**

- **We recommend no maintenance therapy in patients who are dialysis-dependent and have no extrarenal manifestations of disease. (1C)**

KDIGO Guideline---Maintenance therapy (2)

- **Choice of agent for maintenance therapy**
  - **We recommend AZA 1-2 mg/kg/d orally as maintenance therapy. (1B)**
  - **We suggest that MMF, up to 1 g twice daily, be used for maintenance therapy in patients who are allergic to, or intolerant of, AZA.(2C)**
  - **We suggest trimethoprim-sulfamethoxazole as an adjunct to maintenance therapy in patients with upper respiratory tract disease. (2B)**
  - **We suggest MTX (initially 0.3mg/kg/wk, maximum 25mg/wk) for maintenance therapy in patients intolerant of AZA and MMF, but not if GFR is <60 ml/min per 1.73m2. (1C)**
  - **We recommend not using etanercept as adjunctive therapy. (1A)**

Maintenance trials

Name	Design	End point	Result
CYCAZAREM *(EUVAS)* *NEJM 2003*	**AZA v oral CYC**	**Relapse rate**	**No difference in relapse rate**
IMPROVE *(EUVAS)* *JAMA 2010*	**MMF v AZA**	**Relapse free survival**	**MMF less effective than AZA**
WEGENT *NEJM 2008*	**MTX v AZA**	**Adverse event**	**No difference between AZA and MTX**
WGET *NEJM 2005*	**MTX + etanercept (TNF-α) v MTX**	**Remission > 6 missions**	**Etanercept did not improve remission rates**
German Network of Rheumatic Diseases *Rheumatology, 2007*	**Leflunomide v MTX**	**Relapse free survival**	**Leflunomide more effective than MTX**

EUVAS--CYCAZAREM study

- 144 pts achieved remission by oral CTX and pred
  - azathioprine (2mg/kg/day)
  - CTX (1.5 mg/kg/day).
  - Followed-up: 18 months
- Relapse: 15.5% vs. 13.7%, P=0.65.
- Adverse events were comparable

AZA can replace CTX in maintenance therapy

Jayne et al. N Engl J Med 2003;349:36-44

EUVAS- IMPROVE study

- **156 pts achieved remission by induction therapy**
  - **MMF (n=76) 2g/d**
  - **AZA (n=80) 2mg/kg/d**
  - **followed up for a median of 39 months**
- **Relapses: MMF (55.3%) vs AZA (37.5%) (HR 1.69, 95% CI, 1.06-2.70; P=0.03).**

MMF was less effective than AZA for maintenance therapy

JAMA. 2010; 304(21):2381-8.

WEGENT study

- **MTX vs. AZA in maintenance therapy**
- **126 pts achieved remission by induction therapy**
  - **azathioprine (2mg/kg/d, n=63)**
  - **methotrexate (0.3mg/kg/w, up to 25mg/w, n=63)**
  - **for 12 months**
  - **Scr <2mg/dl**
- **Relapse rate and adverse events were comparable**

MTX could be used in mild pts for maintenance therapy

N Engl J Med 2008; 359, 2790-803

Leflunomide (LEF)

- RCT from Germany
- 54 pts with WG achieved remission by induction therapy
  - LEF (30 mg/day)
  - Oral MTX (7.5 mg/w, up to 20 mg/w)
  - Duration: 2 years
- LEF vs MTX
  - More effective in preventing relapses (*P* = 0.037)
  - Higher rate of adverse events.

Rheumatology, 2007; 46, 1087-91

Maintenance trials in progress

Name	Design	End point
REMAIN *(EUVAS) completed in 2010*	**AZA for 48 months v AZA for 18 months**	**Disease-free survival for 48 months**
MAINRITSAN	**RTX 0.5g 6 monthly v AZA**	**Number of major relapses within 28 months**
RITAZAREM *(EUVAS) Start 2013*	**RTX 1g 4 monthly v AZA**	**Time to first relapse**
BREVAS	**Belimumab (BLyS) + AZA v Placebo + AZA**	**Time to first relapse**

The RITAZAREM Trial

- **An international, open label, RCT comparing rituximab with AZA as maintenance therapy in relapsing ANCA-associated vasculitis**
- **Study Design**
  - **160 participants, 1:1**
  - **Rituximab 1000 mg at months 4, 8, 12, 16 and 20**
  - **Azathioprine 2 mg/kg/day from month 4 to 24.**
- **Primary Objective**
  - **To demonstrate the superiority of rituximab against AZA in the prevention of disease flare in AAV patients with relapsing disease.**

- **Trial Chief Investigators: David Jayne and Peter A. Merkel**

KDIGO Guideline---Treatment of relapse

- **We recommend treating patients with severe relapse of ANCA vasculitis (life- or organ threatening) according to the same guidelines as for the initial therapy. (1C)**

- **We suggest treating other relapses of ANCA vasculitis by reinstituting immunosuppressive therapy or increasing its intensity with agents other than CTX, including instituting or increasing dose of corticosteroids, with or without AZA or MMF. (2C)**

KDIGO Guideline---Treatment of resistant disease

- **In ANCA GN resistant to induction therapy with CTX and corticosteroids, we recommend the addition of rituximab (1C), and suggest i.v. immunoglobulin (2C) or plasmapheresis (2D) as alternatives.**

KDIGO Guideline---Monitoring

- **We suggest not changing immunosuppression based on changes in ANCA titer alone. (2D)**

KDIGO Guideline---Transplantation

- **We recommend delaying transplantation until patients are in complete extrarenal remission for 12 months. (1C)**

- **We recommend not delaying transplantation for patients who are in complete remission but are still ANCA-positive. (1C)**

Conclusions (1)

- **ANCA disease is not rare in Chinese**

- **MPO-ANCA are predominant and kidney Involvement is common and sever**

Conclusions (2)

- Conventional drugs can be used more safely, e.g. i.v. CYC induction and AZA maintenance
- Recent trials show that RTX is non-inferior to CYC for induction of remission
- Maintenance therapy with AZA, MMF or MTX is effective, but AZA better than MMF in recent trial
- New therapeutic targets are emerging and need to be tested in clinical trials

Acknowledgement

- 北大医院肾内科
  - 陈旻
  - 徐鹏程（天津医大总院）
  - 袁军（湖北省中医院）
  - 苟慎菊（四川大学）
  - 郝建（内蒙医学院附院）
  - 邢广群（青医附院）
  - 常东元
  - 李志盈
  - 王辰
  - 王环
  - 黄一旻
- University of Groningen
  - CGM. Kallenberg
- Lund University
  - T Hellmark
  - M Segelmark