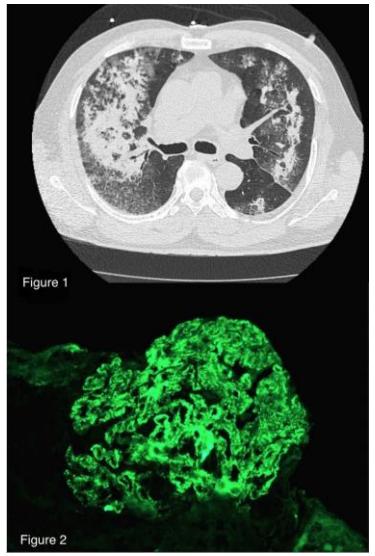
# Update on Pulmonary renal syndrome with vasculitis nature

# (Advanced in therapy)

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- Recent studies have shown that ANCA specificity (PR3 versus MPO) is more important for prognosis, relapse risk, response to therapy and outcomes than the specific diagnosis (GPA versus MPA).
- the presence of PR3-ANCA (rather than MPO-ANCA) portends a better response to rituximab than to cyclophosphamide, but also a much higher relapse risk, and hence the need for ongoing maintenance therapy.
- For patients with EGPA, the presence of ANCA (usually MPO-ANCA) conveys a vasculitic disease phenotype, and glomerulonephritis or DAH is very unusual in the absence of ANCA.

- The reported rates of relapse vary widely among studies, (10 to 60 %).

- differences in induction or maintenance therapy,
- (ANCA) serotype ( [PR3] versus [MPO]),
- the proportion of patients with (GPA) as compared with (MPA),
- the duration of follow-up,
- the criteria used to define relapse.

- patients with GPA are more likely to relapse than those with MPA

- **Risk factors for relapse —**

- ●Seropositivity for PR3-ANCA
- ●Prior history of relapsing disease
- ●Involvement of the lung prior to remission
- ●Involvement of the upper respiratory tract prior to remission
- ●Persistence of elevated ANCA titers, particularly PR3-ANCA, and rising ANCA titers

- **Precipitants of relapse —**

- infections have been hypothesized to trigger some disease flares by inducing expression of the ANCA antigens (PR3 and MPO) on the surface of circulating  neutrophils

- Discontinuation of glucocorticoids may also be associated with a flare.

One meta-analysis, found that patients who participated in trials in which low-dose prednisone

# ESTABLISHING RELAPSING DISEASE

- **Monitoring for relapse**
  - **Patient self-monitoring**
  - **Monitoring by the clinician**
- **Diagnosis of relapse**

- **Non-organ and non-life threatening relapse** – Our approach to the treatment of a mild, non-organ-threatening relapse varies, depending

For patients while still receiving maintenance therapy, we suggest increasing the dose of GC and, when relevant, increasing the dose of the immunosuppressive agent used for maintenance therapy rather than switching to another therapy.

•For patients after maintenance therapy has been discontinued, we suggest reinstitution of the prior maintenance therapy in combination with a short course of GC .Maintenance therapy should be continued for a longer period of time than was given prior to the relapse ( 12 to 18 months if the original course of maintenance therapy was 6 to 12 months).

Patients who have multiple relapses despite treatment with CYC and/or RTX, or who cannot tolerate these therapies, can be treated with MMF.
AZA and MTX are reasonable alternatives

- **●Organ- or life-threatening relapse**

- Cyclophosphamide is a reasonable alternative for patients whose relapse is characterized by advanced and progressive crescentic glomerulonephritis or severe pulmonary disease with massive hemorrhage.

  However, there are no trial data to guide the choice between cyclophosphamide and rituximab in such patients. In addition, some experts treat such patients with **both** cyclophosphamide and rituximab (four weekly infusions of rituximab plus two intravenous pulses of cyclophosphamide)

- **Maintenance therapy after reinduction —**

nts

**Relapse after maintenance therapy** –

For patients who relapse after the discontinuation of the original course of maintenance therapy, we suggest using the same drug for maintenance therapy after remission has been reinduced. However, the duration should be longer than the initial course (12 months or longer if the original course of maintenance therapy was 6 to 12 months). For patients who have frequent relapses, lifelong maintenance therapy may be appropriate, similar to that in recipients of organ transplants

**Relapse during maintenance therapy** –

For patients who exhibit a severe relapse while on the original course of maintenance therapy, we suggest using a different drug for maintenance therapy after reinduction of remission. In such patients, the duration of maintenance therapy may be similar to that suggested for the original course of maintenance therapy (usually 12 to 18 months.

# AAV

- Refractory disease is defined by EULAR as:
- Unchanged or increased disease activity in acute AAV after 4 weeks of treatment with standard therapy in acute AAV

- Lack of response, defined as <50% reduction in the disease activity score BVAS/wegener's granulomatosis (WG)), after 6 weeks of treatment,

- Chronic, persistent disease defined as presence of at least one major or three minor items on the disease activity score after >12 weeks of treatment.

# RESISTANT DISEASE

Treatment-resistant (GPA) or (MPA) refers to active disease that is organ- or life-threatening despite optimal initial immunosuppressive therapy with GC plus either CYC or RTX.

older age

- Some patients are incorrectly considered to be treatment resistant. Alternative diagnoses include permanent tissue damage due to previous inflammatory injury, nonadherence to therapy, inadequate initial immunosuppression, medication toxicity, and infection.

- Treatment-resistant GPA or MPA is diagnosed if one or both of the following are present despite optimal immunosuppressive therapy for an adequate period (usually six months, or three months in a patient who is dialysis dependent):

- •A progressive decline in kidney function (increase in serum CR plus persistence of an active urine sediment )that is judged to be due to active vasculitis or a kidney biopsy that shows active GN
- •Persistence or new appearance of extrarenal manifestations of active vasculitis.

# EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis

M Yates,[1,2] R A Watts,[2,3] I M Bajema,[4] M C Cid,[5] B Crestani,[6] T
B Hellmich,[8] J U Holle,[9] M Laudien,[10] M A Little,[11] R
P A Merkel,[14] J Mills,[15] J Mooney,[1] M Segelm
A Vaglio,[20] N Yalçındağ,[21] D R Jayne,[22]

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► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2016-209133).

For numbered affiliations see end of article.

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**ABSTRACT**

In this article, the 2009 European Le
Rheumatism (EULAR) recommenda
management of antineutrophil
(ANCA)-associated vasculitis
The 2009 recommendatio
of primary small and me
update has been devel
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For a major relapse of organ-threatening or life-threatening disease in AAV we recommend treatment as per new disease with a combination of glucocorticoids and either cyclophosphamide OR rituximab.

Rituximab

Cyclophosphamide

- ●General approach to patients with treatment-resistant GPA or MPA depends upon which immunosuppressive regimen was attempted for initial induction therapy and the extent and severity of the residual active disease:

For patients whose di… with CYC, we

- For … h RTX, we sugges…

For p… CYC for at least 3to 6months but continue to have active disease, we treat with (MMF). Concurrent therapy with both CYC and RTX is a reasonable alternative in patients with life-threatening illness

●Patients with treatment-resistant GPA or MPA have a much worse kidney prognosis than patients who respond. .

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# Update on the management of ANCA-associated vasculitis

RTX has been found superior to CYC for patients positive for PR3-ANCA and for patients with relapsing GPA or MPA and therefore has essentially replaced the use of CYC.

This outcome is also true for patients with DAH requiring mechanical ventilation.

for patients with MPA or MPO-ANCA-associated vasculitis who experience a disease relapse, or for whom fertility preservation or compliance is of concern, RTX is preferable to CYC.

# Efficacy of Rituximab and Plasma Exchange in Antineutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis (AAV) with Severe Renal Disease

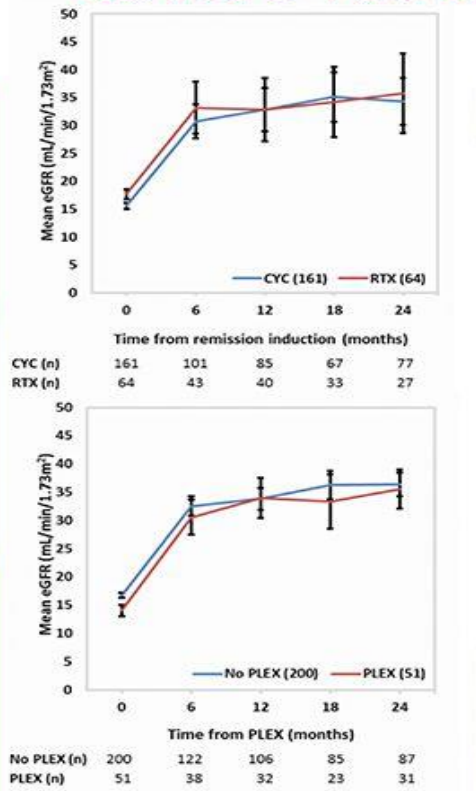
## METHODS

**MPO or PR3–ANCA positive MPA and GPA**
**Severe renal disease**
**(eGFR<30 mL/min/1.73m²)**
**n = 251**

**Rituximab (RTX)**
**vs.**
**Cyclophosphamide (CYC)**
**+/-**
**PLEX**

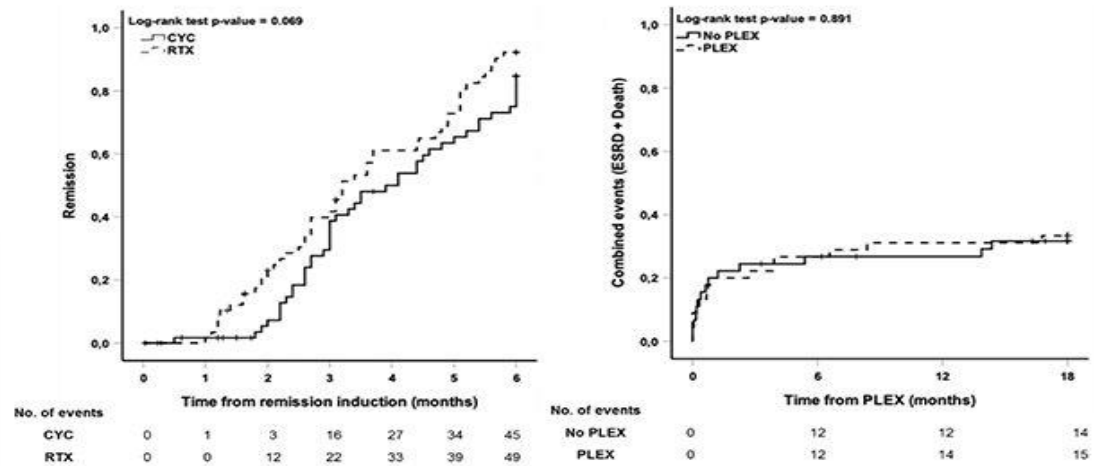
**Propensity Score Matching Analysis**
Treatment related factors
RTX vs. CYC or PLEX status
Treatment with IV MTP
Disease severity related factors
eGFR <15 mL/min/1.73m2
Alveolar Hemorrhage

**Vasculitis outcomes**
**Renal outcomes**




## RESULTS

### Similar renal function recovery




**CYC vs. RTX** **PLEX vs. No PLEX**
**No differences in the outcomes after adjustment by Propensity Score Matching**

**Conclusion:** The apparent benefits and risks of using CYC or RTX for the treatment of patients with AAV and severe renal disease are balanced. The addition of PLEX to standard remission-induction therapy showed no benefit in our cohort. A randomized controlled trial is the only satisfactory means to evaluate efficacy of remission-induction treatments in AAV with severe renal involvement.

doi: 10.1681/ASN.2019111197

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

- Plasma exchange should be considered for patients with AAV and a serum creatine level of >500 µmol/L (5.7 mg/dL) due to rapidly progressive glomerulonephritis in the setting of new or relapsing disease.
-

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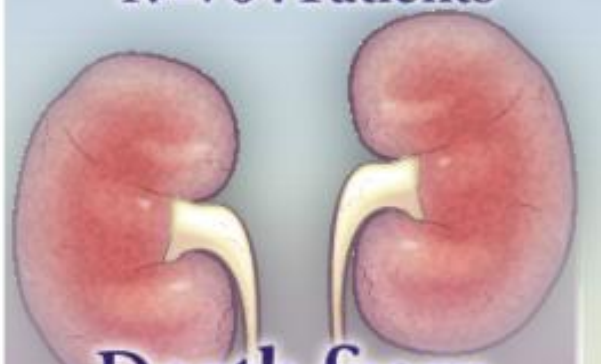
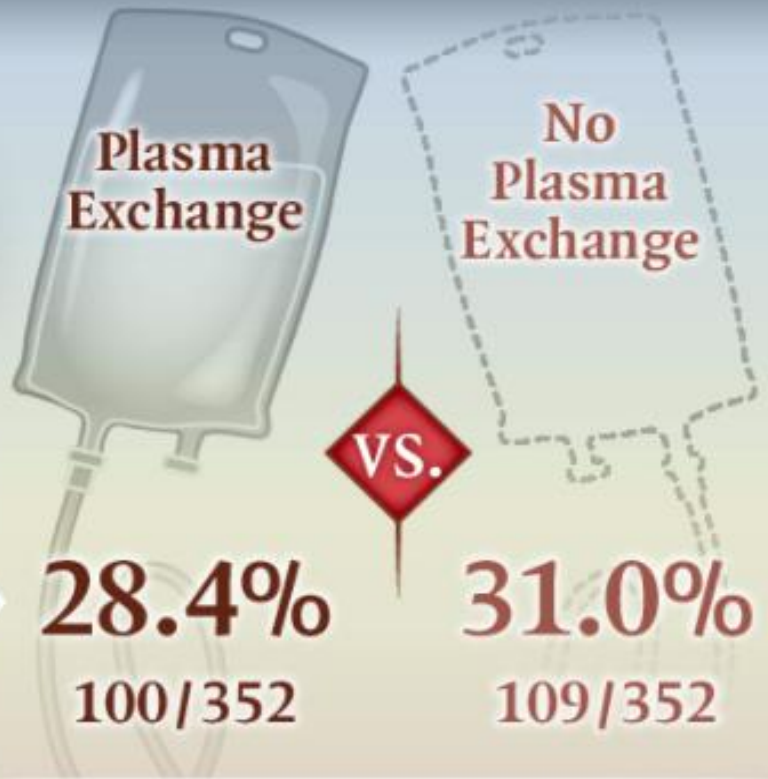
# Plasma Exchange and Glucocorticoids for ANCA-Associated Vasculitis

## PEXIVAS, A MULTICENTER, RANDOMIZED, 2X2 FACTORIAL TRIAL

N=704 Patients



Death from any cause or end-stage kidney disease




28.4% (100/352) vs. 31.0% (109/352)

P=0.27


25.5% (83/325) vs. 27.9% (92/330)

Noninferiority margin, 11 percentage points

# New Therapeutic Targets in ANCA-associated Vasculitis

Maria Prendecki, Stephen P. McAdoo

## Abstract

Anti-neutrophil cytoplasm antibody (ANCA)- associated vasculitis (AAV) is a rare systemic auto-immune disease characterised by necrotizing inflammation of predominantly small blood vessels and the presence of circulating ANCA

has led to the identification of novel therapeutic targets which may address these problems, including those directed at the aberrant adaptive autoimmune response (B and T cell directed treatments) and those targeting innate immune elements (complement, monocytes, neutrophils). It is anticipated that these novel treatments, used alone or in combination, will lead to more effective and less-toxic treatment regimens for patients with AAV in the future.

has led to the identification of novel therapeutic targets which may address these problems, including those directed at the aberrant adaptive autoimmune response (B and T cell directed treatments) and those targeting innate immune elements (complement, monocytes, neutrophils). It is

# Rituximab versus azathioprine as therapy for maintenance of remission for anti-neutrophil cytoplasm antibody-associated vasculitis (RITA
randomized co

Seerapani Gopaluni[1†], Rona M. Sm
Ulrich Specks[3], Peter A. Merkel[2], D

Clinical and epide
Concise report

Rituximab ve
renal vasculi

Rachel B Jones[1], S
Matthew D Morgan[5],
Paassen[2], Michael Wa
(EUVAS)

# Long-Term Outcomes Among Participants in the WEGENT Trial of Remission-Maintenance Therapy for Granulomatosis With Polyangiitis (Wegener's) or Microscopic Polyangiitis

Xavier Puéchal ✉, Christian Pagnoux, Élodie Perrodeau, Mohamed Hamidou, Jean-Jacques Boffa, Xavier Kyndt, François Lifermann, Thomas Papo, Dominique Merrien, Amar Smail, Philippe Delaval, Catherine Hanrotel-Saliou, Bernard Imbert, Chahéra Khouatra, Marc Lambert, Charles Leské, Kim H. Ly, Edouard Pertuiset, Pascal Roblot, Marc Ruivard, Jean-François Subra, Jean-François Viallard, Benjamin Terrier, Pascal Cohen, Luc Mouthon, Claire Le Jeunne, Philippe Ravaud, Loïc Guillevin, for the French Vasculitis Study Group

AJKD

Core Curriculum

# ANCA-Associated Vasculitis: Core

## Novel Approaches to Remission Induction Therapy

### Combining Rituximab and Cyclophosphamide

### Complement Inhibition

Identification of the role of complement in AAV has led to therapies targeting the alternative pathway and the anaphylatoxin C5a. In a phase 2 study, the selective C5a receptor inhibitor avacopan, given with and without low-dose steroid, was compared to

observational studies reported results on the combined use of rituximab with lower dose

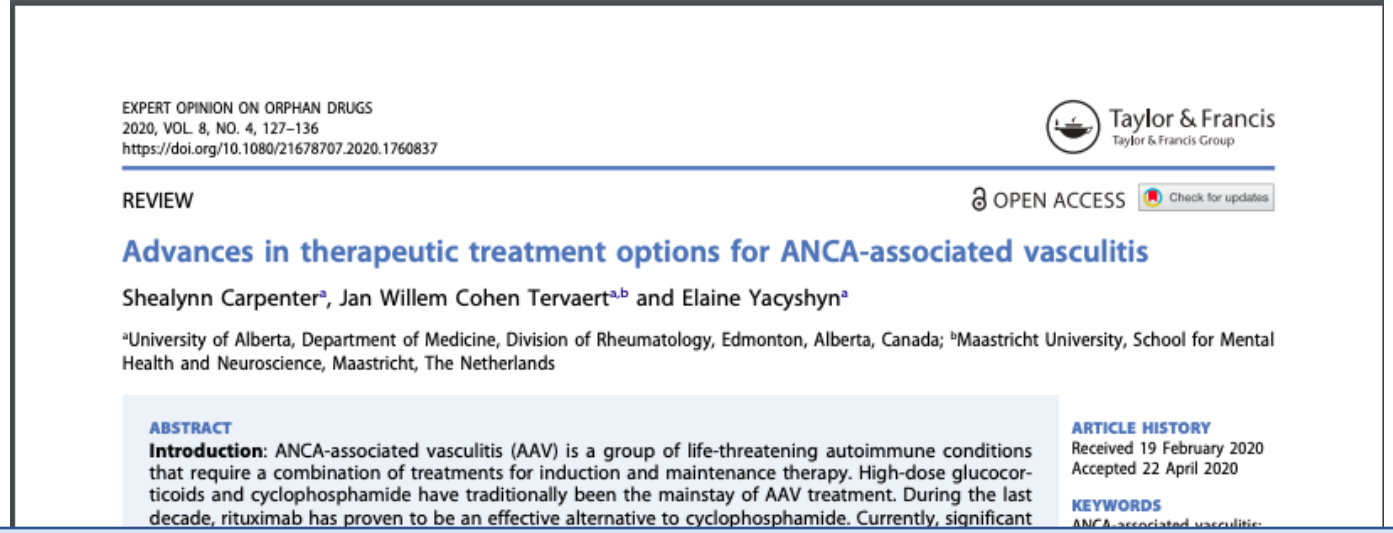
series provides a detailed review of the epidemiology, pathogenesis, diagnosis, and advances in the management of AAV.

2 large observational studies reported results on the combined use of rituximab with lower dose cyclophosphamide (oral or intravenous) using a faster glucocorticoid taper. These studies demonstrated that the combination therapy induced remission in >80% of patients at 6 months and allowed for the use of lower glucocorticoid doses.

# EGPA

- ●For patients with a FFS <2 and suboptimal control of asthma with oral GC or inability to taper oral GC to a tolerable dose, we suggest addition of MEPOLIZUMAB 300 mg every four weeks, as an alternative to immunosuppressive agents.

- ●Defining the role of RTX in EGPA that is resistant to standard therapy requires prospective, randomized trials.



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REVIEW

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## Advances in therapeutic treatment options for ANCA-associated vasculitis

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**ABSTRACT**

**Introduction**: ANCA-associated vasculitis (AAV) is a group of life-threatening autoimmune conditions that require a combination of treatments for induction and maintenance therapy. High-dose glucocorticoids and cyclophosphamide have traditionally been the mainstay of AAV treatment. During the last decade, rituximab has proven to be an effective alternative to cyclophosphamide. Currently, significant

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**KEYWORDS**
ANCA-associated vasculitis;

interleukin-5 (IL-5) antagonists are being investigated as an EGPA specific therapy. IL-5 stimulates eosinophilic activity and has an important role in the pathogenesis of EGPA . Mepolizumab is a humanized monoclonal anti-IL-5 antibody that has been used in two studies as a treatment for EGPA vasculitis.

A therapeutic antibody to the IL-5 receptor benralizumab is also the subject of a current clinical trial in EGPA . Alternatively, omalizumab, an IgE targeting biologic, may be used as a steroid-sparing agent. Specifically, omalizumab can reduce asthma symptoms and exacerbations in patients with EGPA

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ORIGINAL ARTICLE

# Mepolizumab or Placebo for Eosinophilic Granulomatosis with Polyangiitis

M.E. Wechsler, P. Akuthota, D. Jayne, P. Khoury, A. Klion, C.A. Langford, P.A. Merkel, F. Moosig, U. Specks, M.C. Cid, R. Luqmani, J. Brown, S. Mallett, R. Philipson, S.W. Yancey, J. Steinfeld, P.F. Weller, and G.J. Gleich, for the EGPA Mepolizumab Study Team*

ABSTRACT

**BACKGROUND**

Eosinophilic granulomatosis with polyangiitis is an eosinophilic vasculitis. Mepolizumab, an anti–interleukin-5 monoclonal antibody, reduces blood eosinophil counts and may have value in the treatment of eosinophilic granulomatosis with polyangiitis.

**METHODS**

In this multicenter, double-blind, parallel-group, phase 3 trial, we randomly as-

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Wechsler at National Jewish Health, 1400 Jackson St., Denver, CO 80230, or at mikewechsler@gmail.com.

[Mepolizumab is a humanized monoclonal anti-IL-5 antibody that has been used in two studies as a treatment for EGPA vasculitis. Mepolizumab maintenance treatments had a higher remission induction rate, longer remission duration, and lower GC dosing requirements than the placebo group which received only prednisone

# The novel approaches to the treatment of eosinophilic granulomatosis with polyangitis

IFN-α can inhibit eosinophil degranulation and reverse Th2-mediated immune response. IFNα (3 million units, three times a week) was administered in a

Ta
strat IVIG combined with or without plasmapheresis

Om has been reported to be effective in EGPA. Tsuriki-

antibo awa *et al.* [16] have reported that IVIG showed sig-

# Anti GBM disease

- **PATIENTS WITH RECURRENT DISEASE**
- Relapses are uncommon (around 2 percent in one center's experience),
- There may be a higher rate of recurrence in patients who are smokers or have exposure to hydrocarbon in their occupation.

| |
|---|
| In cases of recurrence with kidney involvement, we repeat a kidney biopsy to confirm the diagnosis and exclude concomitant pathologies such as ANCA-associated vasculitis and membranous nephropathy. |
| In confirmed cases of recurrent anti-GBM disease, we retreat with plasmapheresis combined with GC and CYC using the same regimen for initial therapy. |
| RTX or _(MMF) may be considered as alternative therapies to CYC in patients who develop recurrent disease while on cyclophosphamide or are unable to tolerate this drug. |

- **Double-positive anti-GBM and ANCA-associated disease –**

- double-positive patients will require maintenance immunosuppressive therapy for ANCA disease because of the tendency of vasculitis to relapse, treatment with plasmapheresis plus immunosuppressive therapy should be considered for those presenting with dialysis-requiring kidney failure.
- one study that included 41 patients with single-positive anti-GBM disease and 37 double-positive patients reported 12-month renal survival rates of 44 and 53 percent.
- Renal recovery at one year was greater among double-positive patients than among those with anti-GBM disease (29 versus 17 percent).

# Anti GBM disease(Novel&Experimental)

- Immunoadsorption +_ immunosuppression
- Suppress of T CELL involvement(blockade of CD28-B7)

# SLE

- **Resistant disease**
- Resistance and is often due to
- Incomplete adherence or nonadherence with the prescribed immunosuppressive regimen
- or to inadequacy of the prescribed regimen.
- Assessment for the development of complete response usually requires

6-12months more after the initiation of induction therapy.

# SLE

- In general, we treat CYC-resistant patients with _(MMF), and MMF-resistant patients withCYC. The induction and maintenance regimens used in resistant LN are the same as those used for primary therapy. Patients who fail treatment with both CYC and MMF may be tr

- ●The treatment algorithm for patients who have combined proliferative LN and lupus membranous nephropathy that is resistant to initial immunosuppressive therapy is the same as for patients with resistant proliferative LN.

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therapy,

therapy,

•For patients who have failed treatment with or are unable to tolerate both CYC and MMF, we suggest RTX, although randomized trials have not been performed and long-term follow-up is not available

# SLE

- •If CYC was used for induction and the patient is taking AZA for maintenance therapy, many experts choose MMF rather than repeating CYC .Alternatively, a second course of CYC can be used if MMF is poorly tolerated.
- •If MMF was used for induction and the patient is no longer taking maintenance therapy, either MMF or CYC may be used for the treatment of relapse.
- •CYC is preferred if relapse occurs while the patient is still taking MMF for maintenance therapy, or, if the patient is taking a low dose of MMF for maintenance, the dose of this drug can be increased to doses recommended for induction therapy.
- •Patients who continue to relapse, like those with resistant LN, may benefit from a trial of RTX.

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