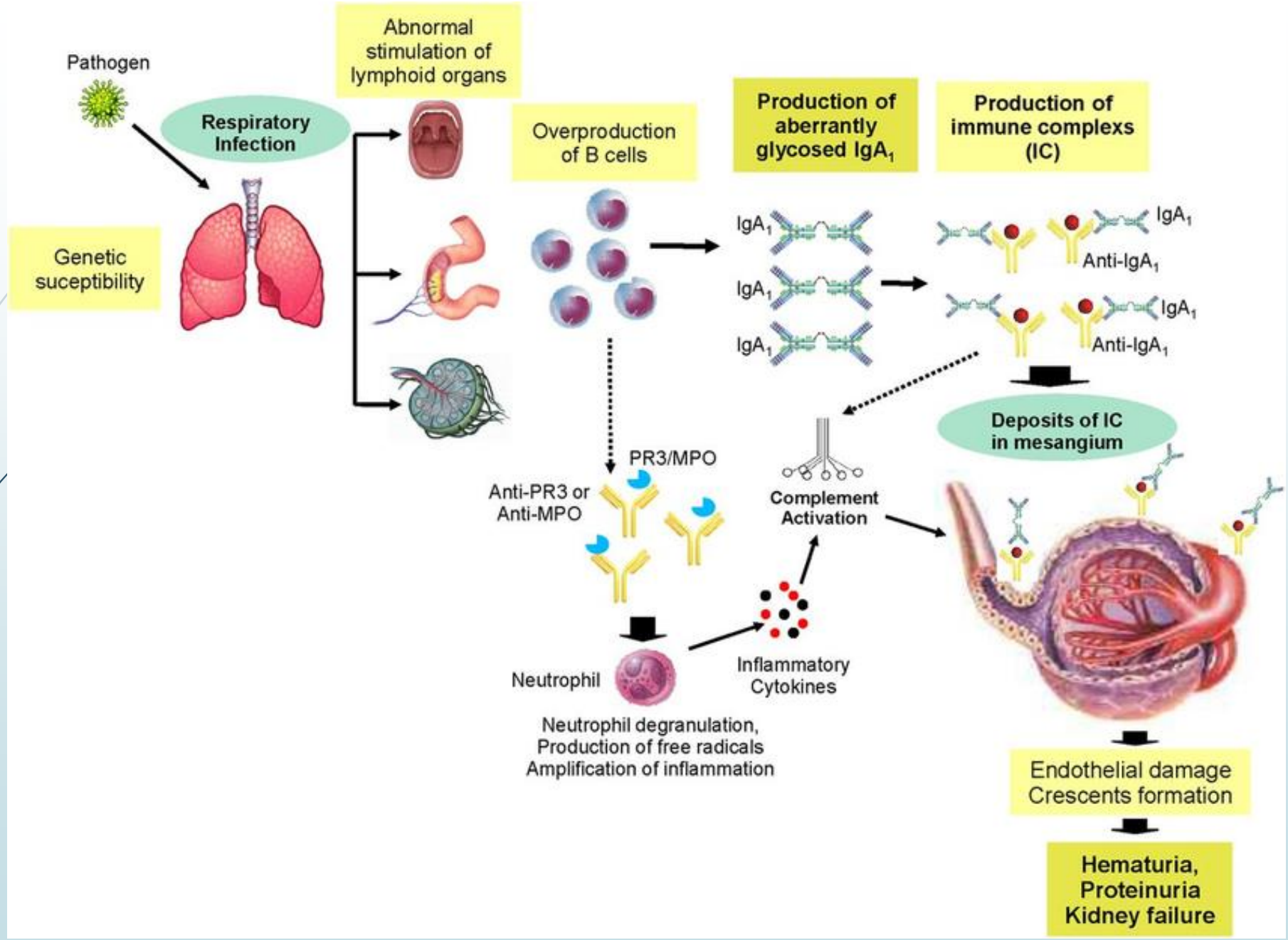
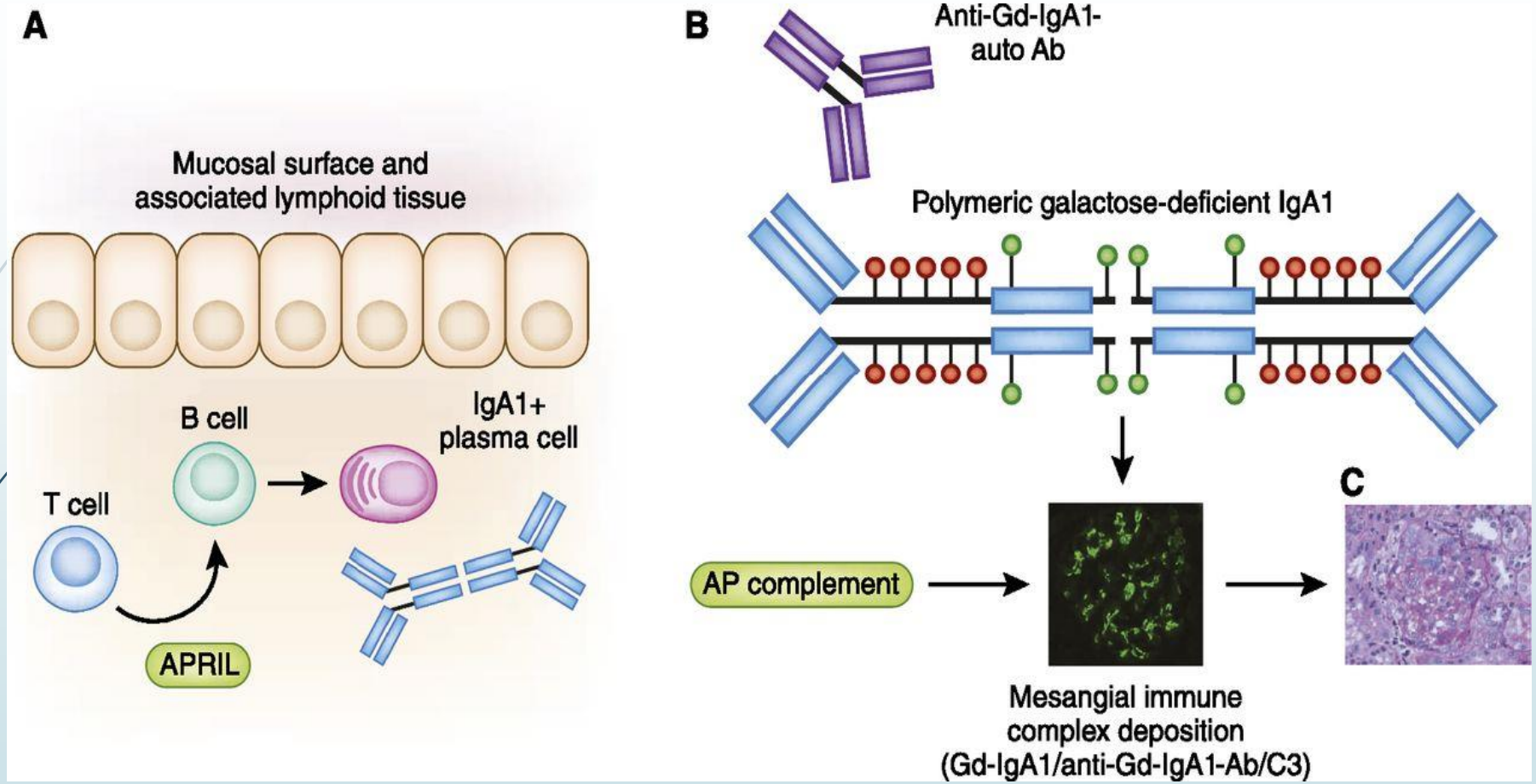
# Rituximab IN IgA Nephropathy

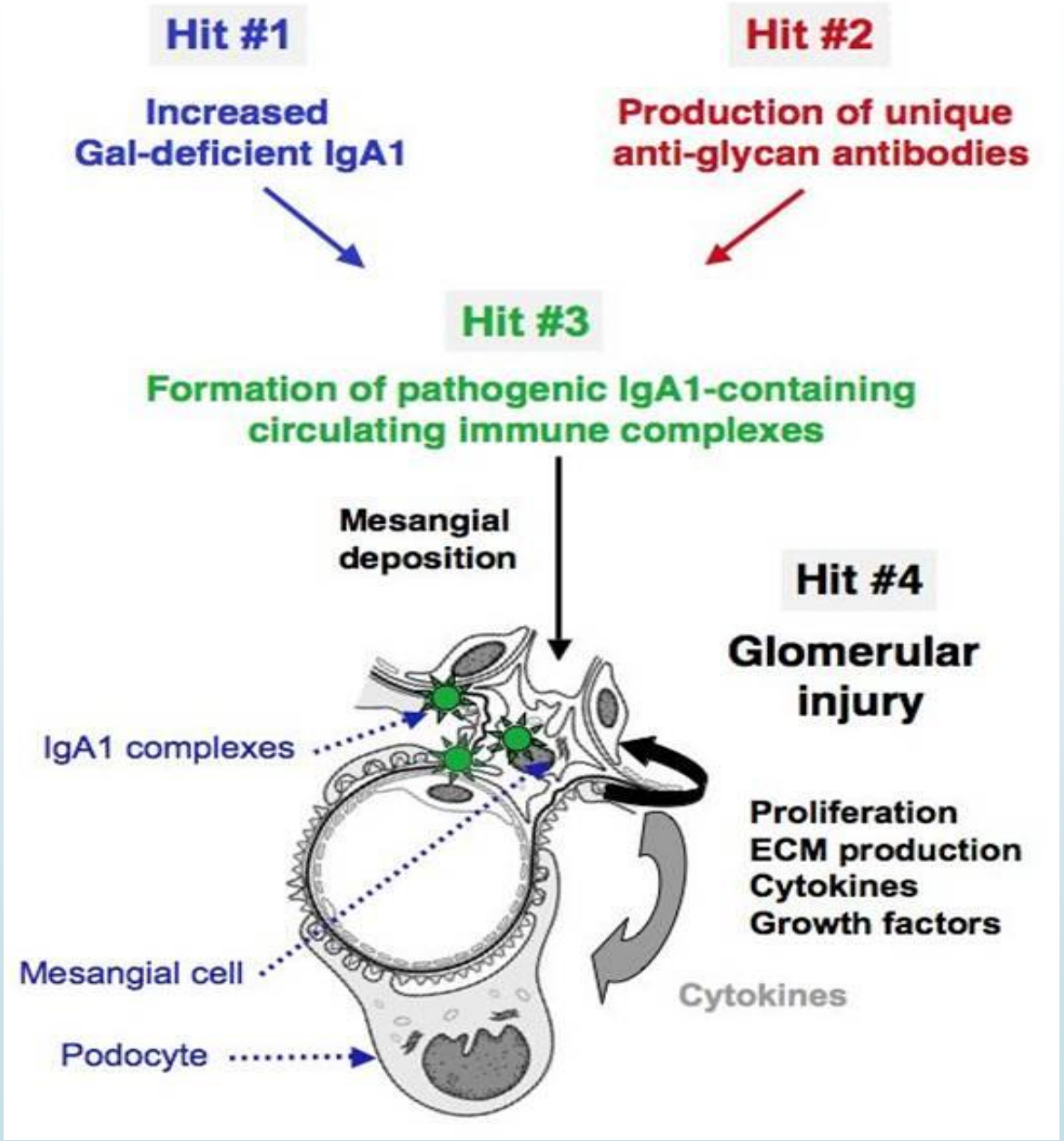
Azadeh Ahmadi

Shahid beheshti university


Pathogen
Respiratory Infection
Genetic suceptibility
Abnormal stimulation of lymphoid organs
Overproduction of B cells
Production of aberrantly glycosed IgA1
Production of immune complexes (IC)
IgA1
IgA1
IgA1
IgA1
Anti-IgA1
IgA1
Anti-IgA1
Deposits of IC in mesangium
PR3/MPO
Anti-PR3 or Anti-MPO
Complement Activation
Neutrophil
Inflammatory Cytokines
Neutrophil degranulation,
Production of free radicals
Amplification of inflammation
Endothelial damage
Crescents formation
Hematuria,
Proteinuria
Kidney failure

- exposure to commensal or pathogenic bacteria is necessary for excess IgA production, and this is facilitated by the presence of mediators of B cell differentiation and proliferation BAFF and/or APRIL.
- It is hypothesized that APRIL contributes to IgAN by promoting B cell class switch to an IgA-producing plasma cell .


A
Mucosal surface and
associated lymphoid tissue
B cell
IgA1+
plasma cell
T cell
APRIL
B
Anti-Gd-IgA1-
auto Ab
Polymeric galactose-deficient IgA1
C
AP complement
Mesangial immune
complex deposition
(Gd-IgA1/anti-Gd-IgA1-Ab/C3)


Hit #1
Increased Gal-deficient IgA1
Hit #2
Production of unique anti-glycan antibodies
Hit #3
Formation of pathogenic IgA1-containing circulating immune complexes
Mesangial deposition
Hit #4
Glomerular injury
IgA1 complexes
Proliferation
ECM production
Cytokines
Growth factors
Mesangial cell
Cytokines
Podocyte

- the **VALIGA, Oxford, and North American cohorts** demonstrated that incorporation of MEST score into predictive algorithms provides timely and accurate predictive accuracy to identify patients at highest risk of poor outcome.
- The combination of MEST and cross-sectional clinical data at biopsy predicted adverse outcome as well as using 2 years of clinical data (proteinuria and mean arterial pressure averaged over a 2-year period).
- This was true regardless of treatment with renin-angiotensin system (RAS) blockade or immunosuppression.

- Independent predictor of the likelihood of developing a combined event of ESRD or a >50% reduction in eGFR:

  -any cellular or fibrocellula crescents

  -eGFR at biopsy

  -time-averaged proteinuria

  - mean arterial pressure

  - Oxford M1, S1, and T1/T2 scores

- The predictive value of all histologic parameters (including crescents) except T1/T2 was lost in patients receiving immunosuppression.

**Table 1** MEST-C criteria in the updated Oxford Classification of IgA Nephropathy

Table 1 | **MEST-C criteria in the updated Oxford Classification of IgA Nephropathy**[3]

| Histological variable | Definition | Score |
|---|---|---|
| Mesangial hypercellularity | More than four mesangial cells in any mesangial area of a glomerulus | • M0: <50% of glomeruli showing mesangial hypercellularity<br>• M1: >50% of glomeruli showing mesangial hypercellularity |
| Endocapillary hypercellularity | Hypercellularity due to an increased number of cells within glomerular capillary lumina | • E0: no endocapillary hypercellularity<br>• E1: any glomeruli showing endocapillary hypercellularity |
| Segmental glomerulosclerosis | Adhesion or sclerosis (obliteration of capillary lumina by matrix) in part but not the whole glomerular tuft | • S0: absent<br>• S1: present in any glomeruli |
| Tubular atrophy/ interstitial fibrosis | Estimated percentage of cortical area showing tubular atrophy or interstitial fibrosis, whichever is greater | • T0: 0–25% of cortical area<br>• T1: 26–50% of cortical area<br>• T2: >50% of cortical area |
| Cellular or fibrocellular crescents | Percentage of glomeruli with cellular or fibrocellular crescents | • C0: absent<br>• C1: 0–25% of glomeruli<br>• C2: ≥25% of glomeruli |

M, mesangial hypercellularity; C, crescents; E, endocapillary hypercellularity; S, segmental glomerulosclerosis; T, tubular atrophy/interstitial fibrosis. Modified with permission from Macmillan Publishers Limited © Roberts, I. S. D. *Nat. Rev. Neph.* **8**, 445–454 (2014).

Markowitz, G. (2017) Updated Oxford Classification of IgA nephropathy: a new MEST-C score
*Nat. Rev. Nephrol.* doi:10.1038/nrneph.2017.67

- the pathology score combined with clinical data account for only a minority (<30%) of the variability in outcome in patients with IgAN
- A majority of the variability in outcome is attributable to unmeasured factors which would hopefully include therapeutic intervention.

- risk factors:
  - -Proteinuria ≥ 1 gr
  - -male sex
  - -Hypertension
  - -Clearance<60 ml/min per 1.73 m2
  - -Glomerulosclerosis
  - -tubulo-interstitial fibrosis
  - -≥ 25% of glomeruli affected by crescents

# Treatment Strategies:

## Conservative Therapy:

- RAS blockade
- Statins : fluvastatin
- Obesity : contribute to proteinuria, overweight/obese group had a worse eGFR and a greater prevalence of CKD stage 3 or greater
- smoking cessation
- Fish oil

# Corticosteroids:

- Exposure to corticosteroids for a 6-month period may have a "legacy effect," with sustained reduction in the risk of progressive renal dysfunction.

- The STOP-IgAN study → the long-term benefits of a 6-month course of corticosteroids → in patients with persistent proteinuria an eGFR>30 ml/min per 1.73 m2 after a 6-month run-in period that involved adequate BP control and RAS blockade … → Patients receive corticosteroids if the eGFR was >60 ml/min per 1.73 m2 , and cyclophosphamide followed by azathioprine if the eGFR of 30–59 ml/min per 1.73 m2

- **The investigators concluded that renal benefit is likely but will need to be weighed carefully against risk.**

# MMF:

- **These studies are limited by small sample size.**
- **It also remains possible there is race-specific variability in response to MMF as in lupus nephritis.**

# Novel Agents:

- **oral budesonide (Nefecon)** → is proposed to act locally at the mucosal lymphoid tissue in the distal ileum and proximal large intestine to modulate IgA production

High firstpass metabolism also theoretically minimizes systemic effects.

More adverse events were seen in the budesonide group, necessitating treatment cessation in 22% of patients on this higher dose.

- **A purified form of adrenocorticotropic hormone**
- **Bortezomib**
- **fostamatinib**

# The VALIGA analysis:

- **suggests that the greatest benefits of corticosteroids may be accrued in patients with the highest degree of proteinuria, particularly >3 g/d**
- **suggests a graded benefit of corticosteroids according to time-averaged proteinuria before treatment, with no difference in renal function decline below 1 g/d of proteinuria.**
- **Therefore, patients with persistent proteinuria<1 g/d likely do not derive significant benefit from addition of corticosteroids.**
- **The 1–3 g/d category remains a "gray zone." Indeed, a long duration of follow-up will be required to demonstrate any potential benefit, based upon rates of renal function decline typically observed in patients with this degree of persistent proteinuria**

CLINICAL RESEARCH www.jasn.org

# A Randomized, Controlled Trial of Rituximab in IgA Nephropathy with Proteinuria and Renal Dysfunction

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## ABSTRACT

IgA nephropathy frequently leads to progressive CKD. Although interest surrounds use of immunosuppressive agents added to standard therapy, several recent studies have questioned efficacy of these agents. Depleting antibody–producing B cells potentially offers a new therapy. In this open label, multicenter study conducted over 1-year follow-up, we randomized 34 adult patients with biopsy–proven IgA nephropathy and proteinuria >1 g/d, maintained on angiotensin–converting enzyme inhibitors or angiotensin receptor blockers with well controlled BP and eGFR<90 ml/min per 1.73 $m^2$, to receive standard therapy or rituximab with standard therapy. Primary outcome measures included change in proteinuria and change in eGFR. Median baseline serum creatinine level (range) was 1.4 (0.8–2.4) mg/dl, and proteinuria was 2.1 (0.6–5.3) g/d. Treatment with rituximab depleted B cells and was well tolerated. eGFR did not change in either group. Rituximab did not alter the level of proteinuria compared with that at baseline or in the control group; three patients in each group had ≥50% reduction in level of proteinuria. Serum levels of galactose-deficient IgA1 or antibodies against galactose-deficient IgA1 did not change. In this trial, rituximab therapy did not significantly improve renal function or proteinuria assessed over 1 year. Although rituximab effectively depleted B cells, it failed to reduce serum levels of galactose-deficient IgA1 and antigalactose–deficient IgA1 antibodies. Lack of efficacy of rituximab, at least at this stage and severity of IgA nephropathy, may reflect a failure of rituximab to reduce levels of specific antibodies assigned salient pathogenetic roles in IgA nephropathy.


*J Am Soc Nephrol* 28: ●●●–●●●, 2016. doi: 10.1681/ASN.2016060640

- Patients were randomly assigned to either continue on standard care, which included a minimum of 3 g of fish oil per day (*n* = 17), or to receive an additional 1 g rituximab at weeks 0, 2, 26 and 28 (*n* = 17).
- **Complete depletion of B cells (CD19+ cells)** was maintained in the vast majority of patients in the rituximab group **over the 12 months**.

- Despite randomization, the possibility exists that patients with more advanced renal disease were assigned to the rituximab group, and that such patients might be less responsive to B-cell depletion than patients with earlier stages of the disease.

- Second, despite highly effective depletion of B cells with rituximab, the fact that neither circulating levels of galactose-deficient IgA1 nor IgG autoantibodies to this particular IgA1 were reduced at 6 months or 12 months comes .
- Autoantibody-producing plasma cells are CD20 negative and are thus not targeted by rituximab .
- these diseases differ in terms of the prominent involvement of the mucosal, in particular intestinal, immune system in IgAN . So perhaps B cells derived from these different compartments differ in their responsiveness to rituximab.

- **Third: immunosuppression in IgAN in general has become more questionable**
- **In STOP-IgAN trial : eGFR outcomes were not improved by adding immunosuppression to optimized supportive care.**

REVIEW

# An update on the treatment of IgA nephropathy

*Sean Barbour*[a,b] *and John Feehally*[c]

**Purpose of review**

The treatment of IgA nephropathy (IgAN) has been limited by several controversies in the literature, including the benefits of corticosteroids in addition to optimized renin–angiotensin system blockers (RASBs), in those with lower estimated glomerular filtration rate (eGFR), or in different ethnic groups. Recent studies have attempted to address these issues.

- **Additional trials demonstrate the potential efficacy of enteric-budesonide but not rituximab on proteinuria reduction, and conflicting findings with mycophenolate mofetil.**

- The **NEFIGAN trial** has been presented in abstract format, and compared enteric budesonide with placebo.
- The treatment group experienced not only a significant reduction in proteinuria, but also a substantial risk of steroid related adverse events suggesting that there may be more systemic drug exposure than anticipated.

www.nephropathol.com DOI: 10.15171/jnp.2018.03 J Nephropathol. 2018;7(1):7-10

Journal of Nephropathology

# Is it the time to offer rituximab as a cost-benefit treatment for immunoglobulin A nephropathy? A short-review to current concepts

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## ABSTRACT

*Context:* IgA nephropathy (IgAN) as an autoimmune disease is the most common cause of glomerulonephritis worldwide. Rituximab effectively depletes B cells and reduces serum levels of IgA1 antibodies. This paper aimed to review the potential benefit of rituximab used in clinical practice of IgAN patients.

*Evidence Acquisitions:* PubMed, EBSCO, Web of Science, directory of open access journals (DOAJ), EMBASE, and Google Scholar were searched for the keywords of IgA nephropathy, rituximab, B cell depletion and autoimmune diseases.

*Results:* Rituximab therapy improved in nephropathies and in recurrent IgAN in several studies. The mechanisms of rituximab therapy in IgAN are unknown. However, a direct effect of rituximab on podocytes by cytoskeleton stabilization is possible. Additionally a possible effect of rituximab on B cells in IgAN may lead to its beneficial impact.

*Conclusions:* This short-review demonstrates that rituximab therapy may be an effective treatment option in IgAN patients, particularly for histological signs of active inflammation. However, results of safety and efficacy of rituximab in IgAN are limited, and definitive conclusions will require further studies. Thus, multicenter clinical trials for safety and efficacy of rituximab therapy are necessary.

- ***The mechanisms of rituximab therapy in IgAN :***
  - **A direct effect on podocytes by cytoskeleton stabilization**
  - **A possible effect on B cells**
  - **A direct modulation of T cell activity**

Immunol Res
DOI 10.1007/s12026-016-8827-5

THERAPEUTIC ASPECTS IN AUTOIMMUNITY

# Rituximab therapy for IgA-vasculitis with nephritis: a case series and review of the literature

**Roberta Fenoglio[1] · Carla Naretto[1] · Bruno Basolo[1] · Giacomo Quattrocchio[1] · Michela Ferro[1] · Paola Mesiano[1] · Giulietta Beltrame[1] · Dario Roccatello[1]**

**Dario Roccatello**

**Abstract** Henoch–Schonlein purpura, also called IgA-vasculitis, is a systemic small vessels vasculitis with immunoglobulin A1-dominant immune deposits. The optimal treatment remains controversial. Because IgA-vasculitis is characterized by leukocyte infiltration of the blood vessel walls along with immunoglobulin A deposition, and because glucocorticosteroids inhibit inflammatory processes, early administration of glucocorticosteroids has been postulated to be effective, but this indication remains controversial. Immunosuppressive agents (azathioprine, cyclophosphamide, cyclosporine, mycophenolate) have been used in combination with glucocorticosteroids without definitive evidence of effectiveness. The efficacy of rituximab in adult IgA-vasculitis has been reported in few cases. We described a monocentric experience on the use of rituximab in adult IgA-vasculitis with biopsy-proven nephritis. The patients achieved a complete remission of nephritis and syndromic manifestations, and no patients experienced adverse reactions. These data have been compared with the limited literature nowadays available.

**Table 1** Patient data

| Patients ($n$°) | Gender | Age at diagnosis | Therapy before RTX | Organ involvement | Follow-up |
|---|---|---|---|---|---|
| 1 | F | 70 | CS, MMF, IGIV | S, K, J° | 8 years |
| 2 | M | 21 | CS, Cyp, CyA, AZA, IGIV, MMF | A, K, S* | 33 months |
| 3 | M | 43 | – | A, K, S, J° | 18 months |
| 4 | F | 26 | C | K, S*, J | 7 months |
| 5 | M | 55 | – | K, A, J, S | 3 months |

*CS* corticosteroids, *MMF* mycophenolate mofetil, *IGIV* intravenous immunoglobulins, *Cyp* cyclophosphamide, *CyA* cyclosporine, *AZA* azathioprine, *S* skin with (*) necrotic ulcers, *A* abdomen, *K* kidney, *J* joint involvement with (°) frank arthritis

**Table 2** Summary of the studies reporting the use of RTX in HSP

| Author (Refs.) | Study design | Numbers of patients treated with RTX | Year of publication | Dosage of RTX | Reason for administering RTX |
|---|---|---|---|---|---|
| Bellan et al. [40] | Case report | 1 | 2015 | 4 weekly RTX (375 mg/m$^2$) | Disease relapse |
| Ishiguro et al. [41] | Case report | 1 | 2013 | 4 weekly RTX (375 mg/m$^2$) | Persistent proteinuria |
| PindiSala et al. [42] | Case report | 1 | 2014 | Two iv infusions of 1000 mg given 2 weeks apart | Disease relapses and corticosteroid dependence |
| Pillebout et al. [19] | Case report | 1 | 2011 | Two iv infusions of 1000 mg given 2 weeks apart | Fist-line therapy |
| Donnithorne et al [43] | Case series (pediatric) | 3 | 2009 | Two iv infusions of 1000 mg given 2 weeks apart | No response to previous treatment |
| Fenoglio et al. (present study) | Case series | 5 | 2016 | AR or Lymphoma protocols | No response or intolerance to previous treatment/first-line therapy |

- RTX, by depleting B cells, might reduce the formation of IgA containing immuno complexes and limited IgAV disease activity.
- The existing reports suggest RTX to be not only an effective treatment in severe and refractory HSPN but also a firstline therapy, and with high chance of long-lasting remission.

Clinical Kidney Journal Advance Access published December 13, 2016

CLINICAL KIDNEY JOURNAL


*Clinical Kidney Journal*, 2016, 1–7

doi: 10.1093/ckj/sfw106
Original article

# B cell–depleting therapy with rituximab or ofatumumab in immunoglobulin A nephropathy or vasculitis with nephritis

Sigrid Lundberg, Emelie Westergren, Jessica Smolander and Annette Bruchfeld

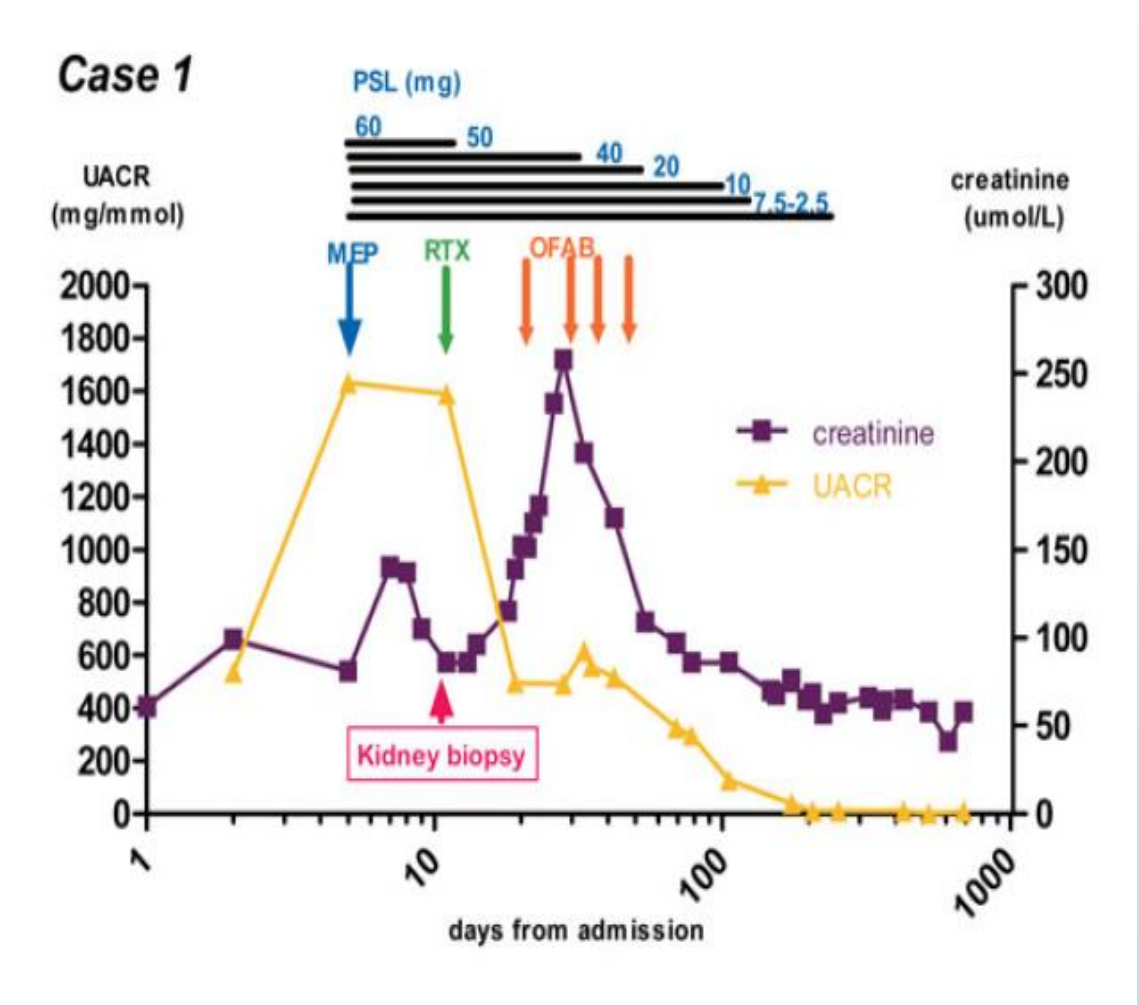
**Methods:** We describe clinical outcomes after 17–22 months in four adult patients with biopsy-confirmed IgAVN or IgAN treated with RTX or OFAB as well as CS soon after diagnosis. All presented with nephritic–nephrotic syndrome and one had crescentic IgAN. Rebiopsy was performed in two cases.

**Results:** RTX and OFAB were well tolerated. Albuminuria was <250 mg/day in three patients at last evaluation and two regained normal renal function. In all cases, renal function improved after therapy. In one patient with severe IgA vasculitis, rebiopsy showed disappearance of subendothelial but not mesangial immune complexes. In the case with crescentic IgAN, rebiopsy after 9 months showed no active necrotic lesions.

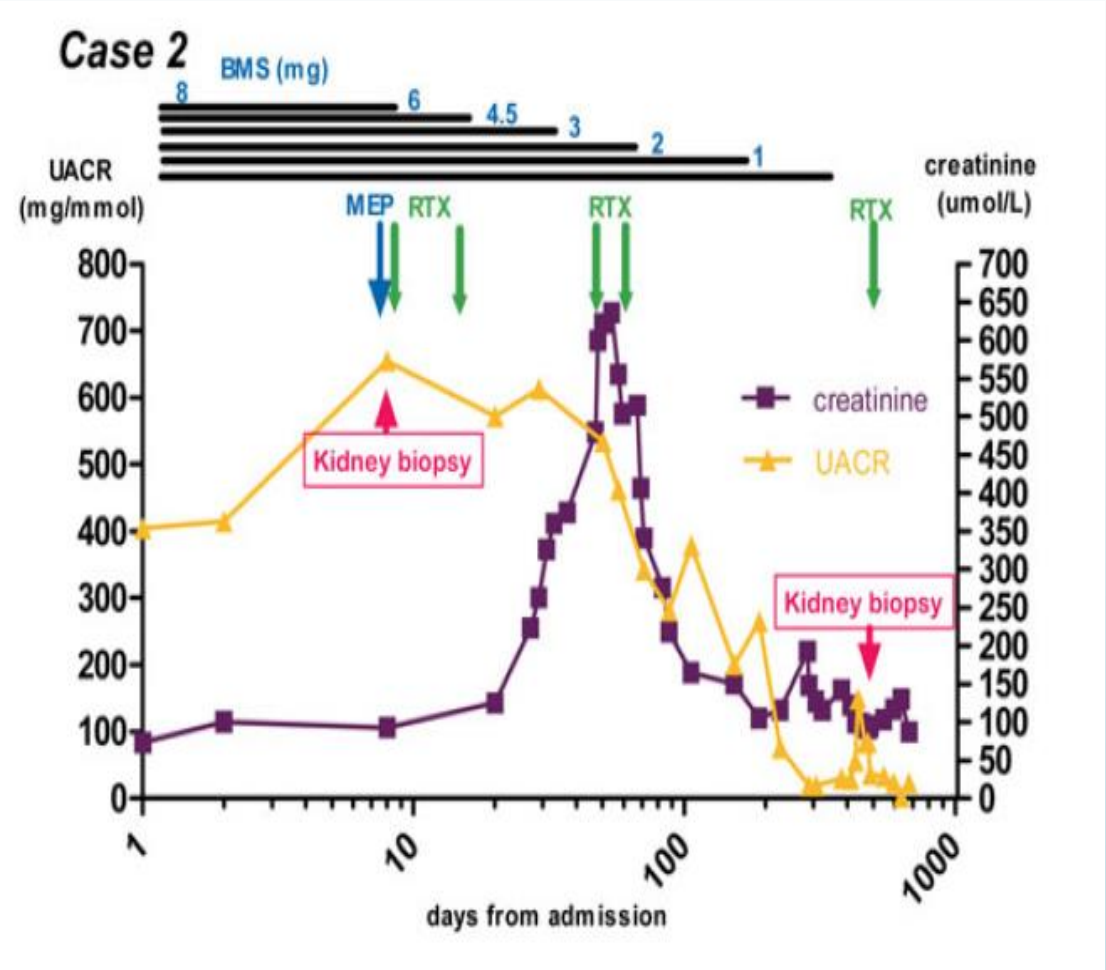
**Conclusions:** B cell–depleting therapy may be an alternative treatment for patients with IgAN or IgAVN and nephritic–nephrotic syndrome. A possible CS-sparing effect should be further evaluated in randomized controlled clinical trials.

**Key words:** Henoch–Schönlein purpura with nephritis, IgA nephropathy, IgA vasculitis, ofatumumab, rituximab

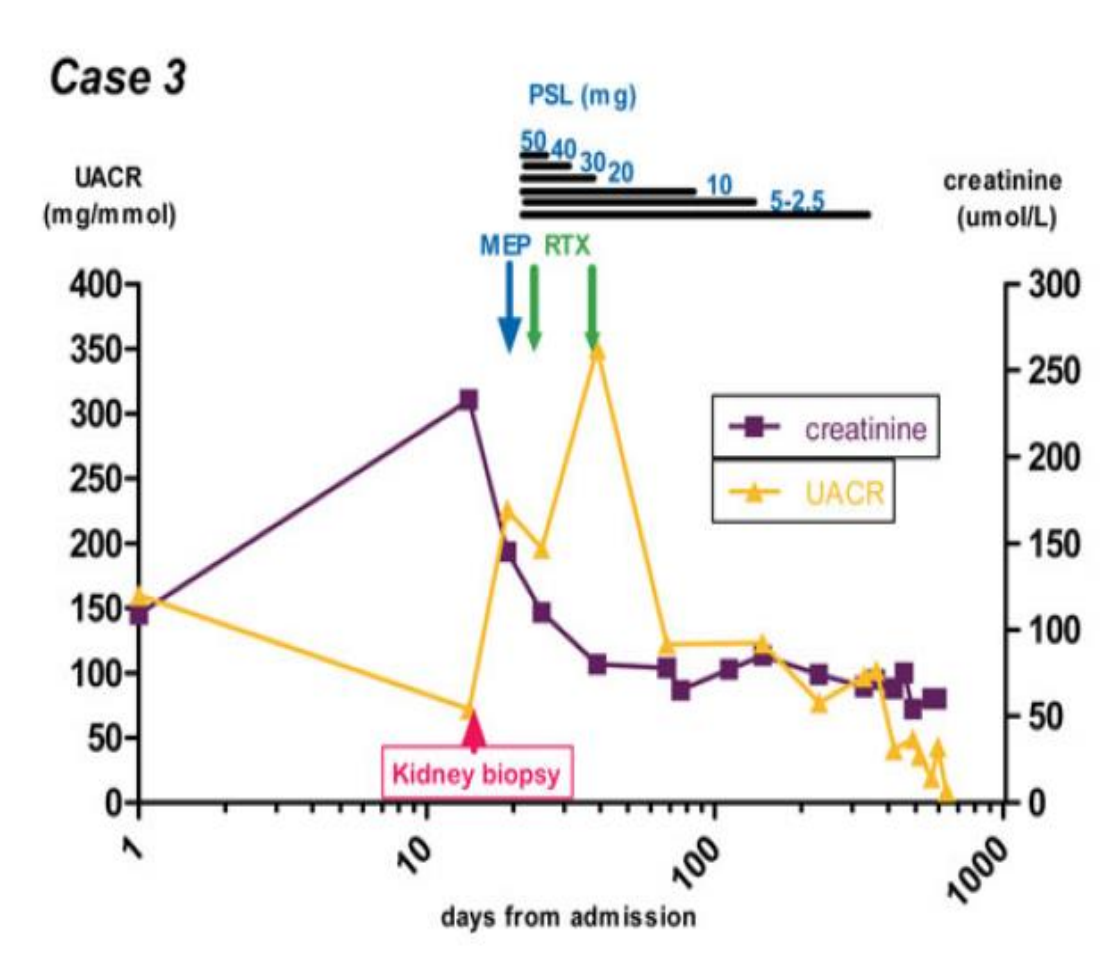
A 19-year-old obese woman with a history of purpura in childhood sought medical attention due to purpura,abdominal pain and arthralgia. Renal biopsy confirmed a diagnosis of IgAVN( **M1S0E1T0** )



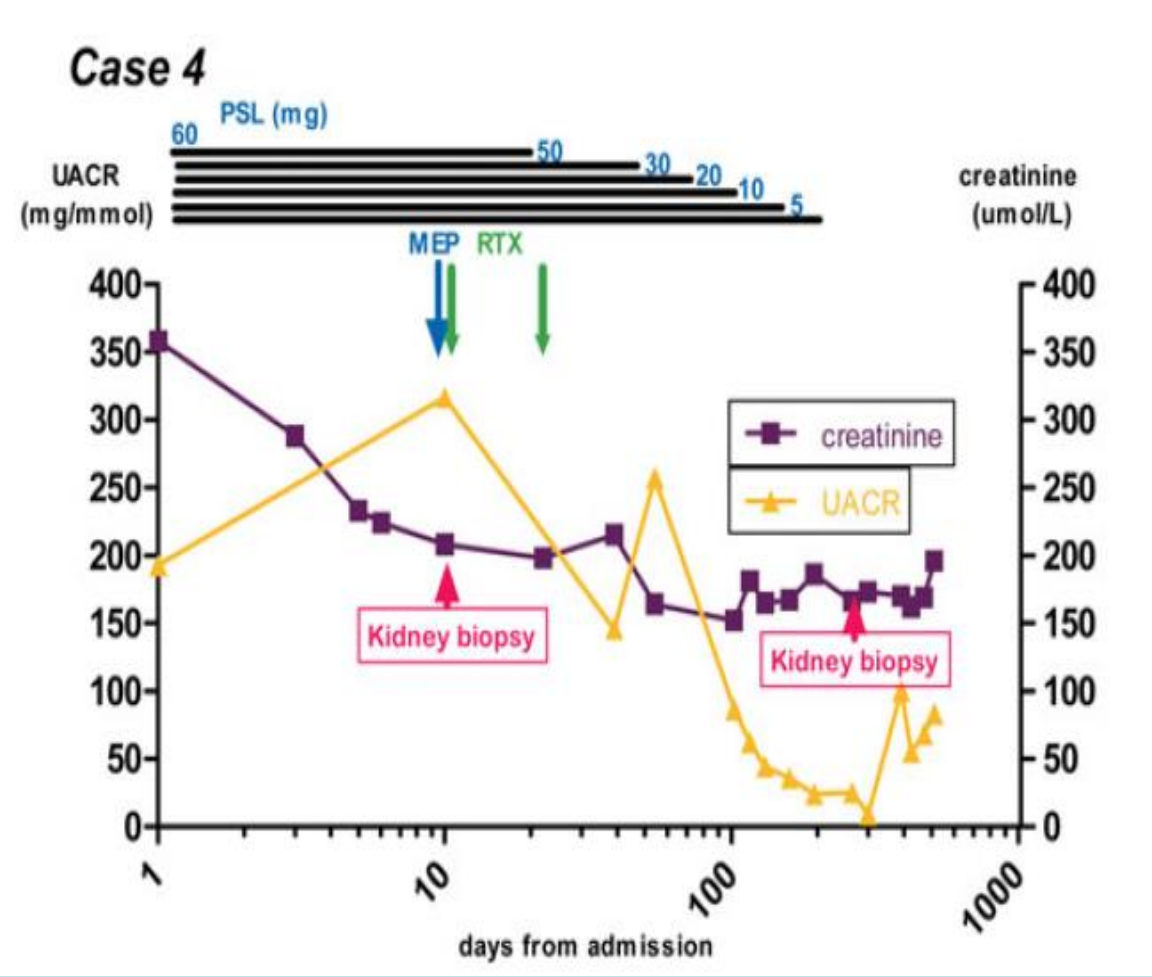
A 49-year-old female smoker with a history of asthma and severe eczema presented with abdominal pain, hematochezia,purpura, mild eosinophilia, edema and a BP of 120/70mmHg. A skin biopsy showed leukocytoclastic vasculitis with negative IF. Rnal biopsy ( **M0E1S0T0** )

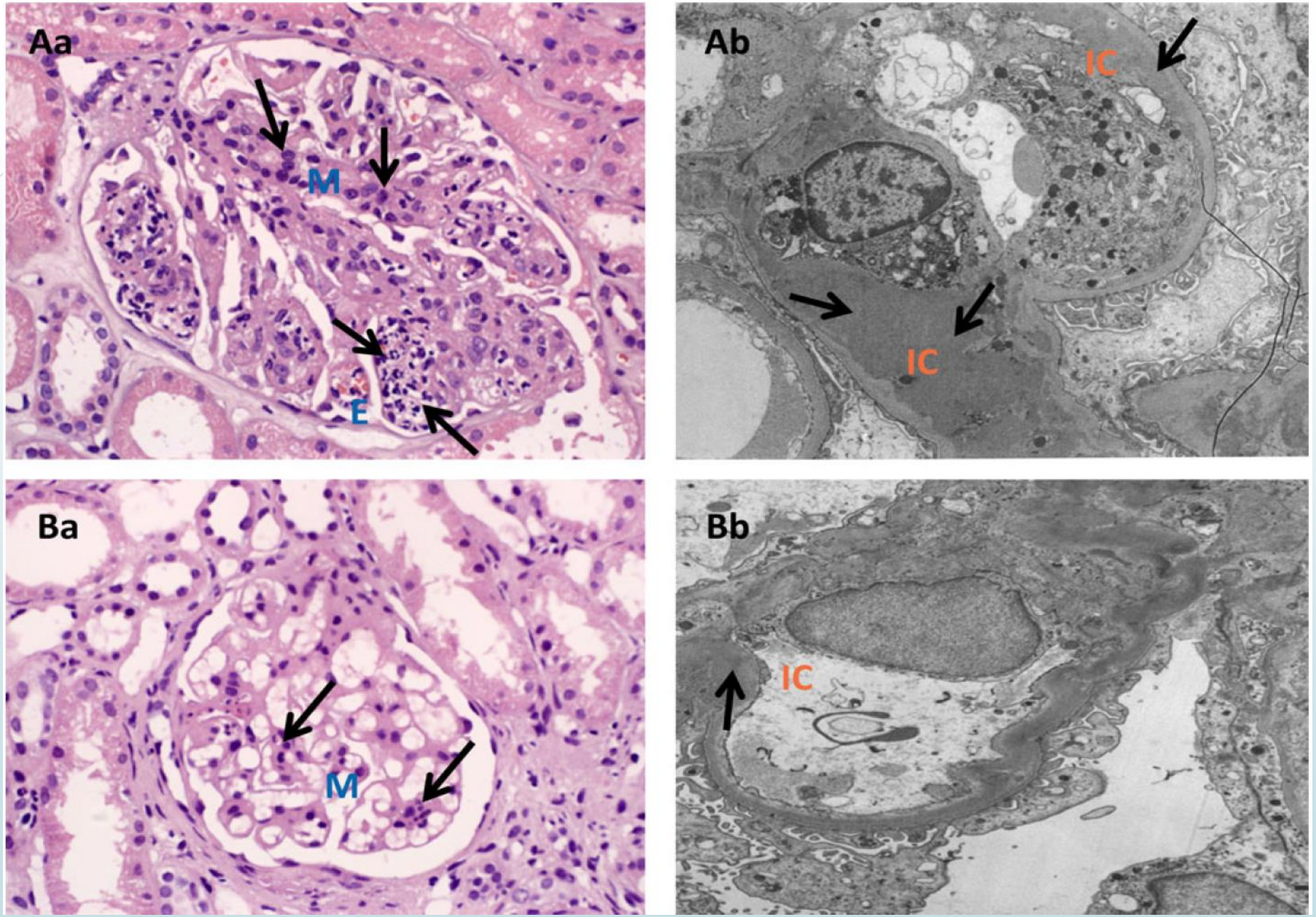


A 28-year-old woman with a family history of IgAN presented with macrohematuria,fever and an unspecific skin rash on her buttocks. Histopathologic examination revealed a diagnosis of IgAN with cellular crescents in 5 of 17 glomeruli (31%)with an Oxford classification ( **M1E0S1T1** ).



A 19-year-old man was admitted to hospital due to fever, a sore throat, macrohematuria and a creatinine of 228 μmol/L (normal for men <100 μmol/L). The Oxford classification was ( **M1E1S1T0** ).




Aa
M
E
Ab
IC
IC
Ba
M
Bb
IC

# Rituximab for Recurrent IgA Nephropathy in Kidney Transplantation: A Report of 3 Cases and Proposed Mechanisms

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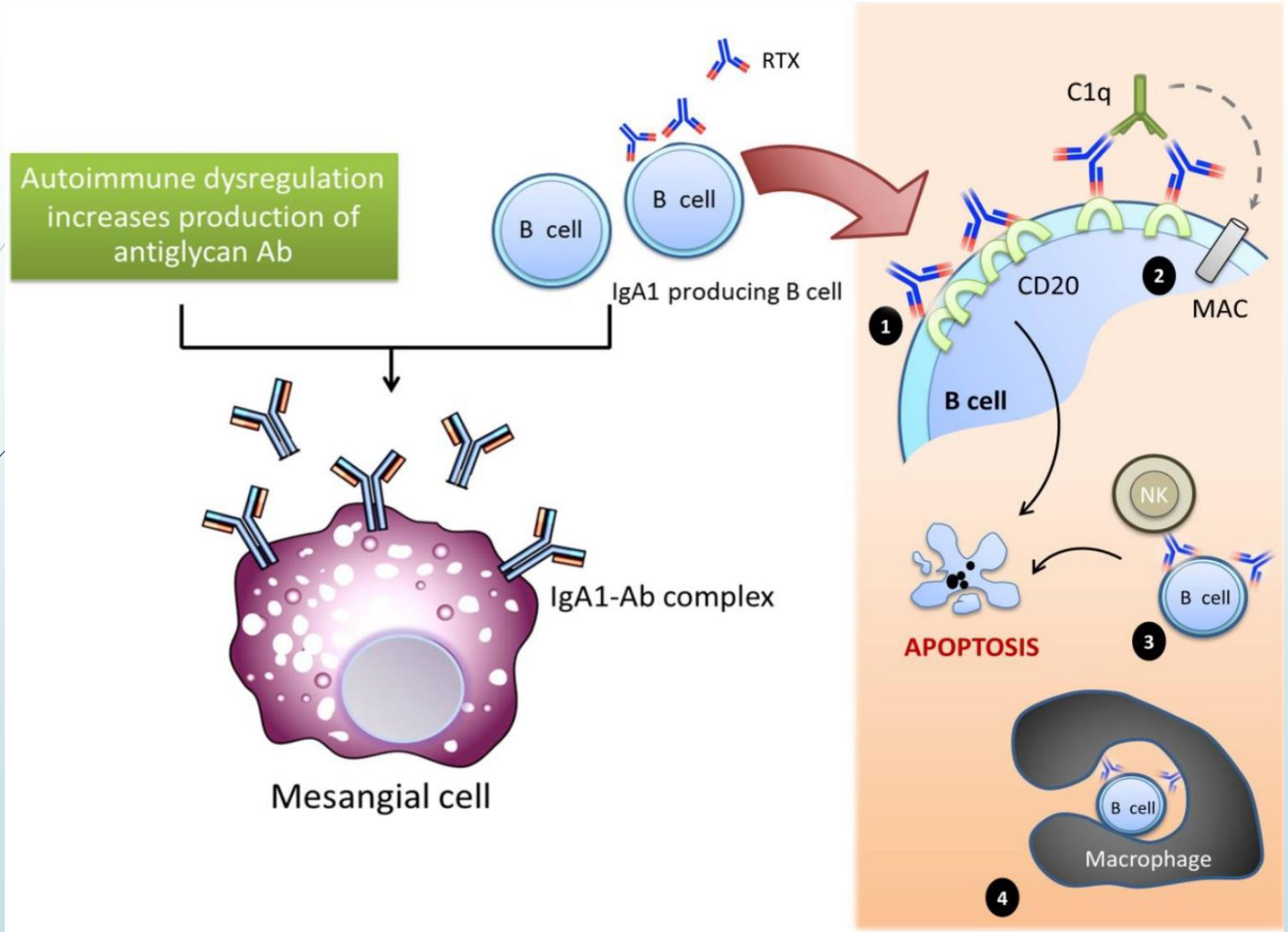
Talerngsak Kanjanabuch, MD[1]; Yingyos Avihingsanon, MD[1,2];

Kearkiat Praditpornsilpa, MD[1]; Somchai Eiam-Ong, MD[1]

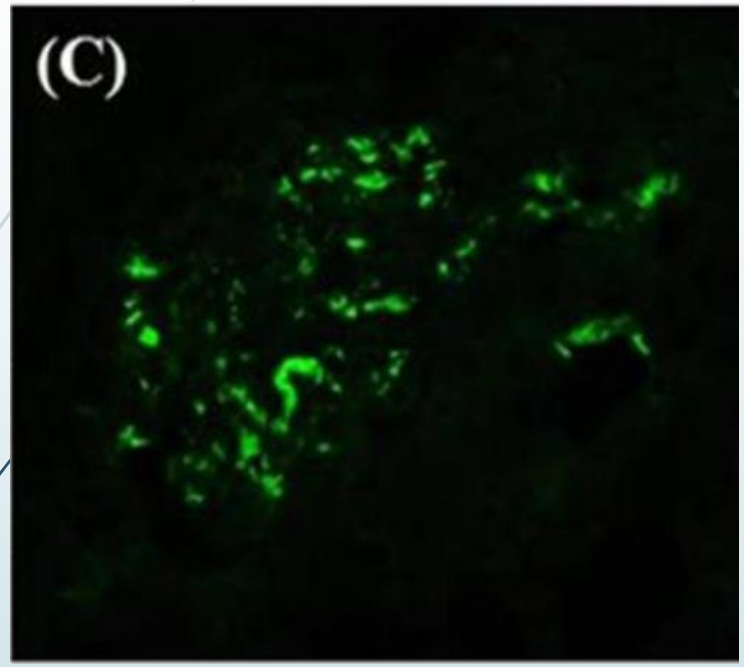
**Methods:** We have reported 3 kidney-transplanted recipients with biopsy-proven recurrent IgAN treated with 4 consecutive months of rituximab at the dose of 375 mg/1.73m$^2$ without corticosteroids.

**Results:** At median follow-up 20 months following rituximab administration, all of 3 recipients demonstrated decrease in proteinuria severity, slow disease progression with a well-tolerated condition. This therapeutic effect is most probably mediated by the B cell depletion.

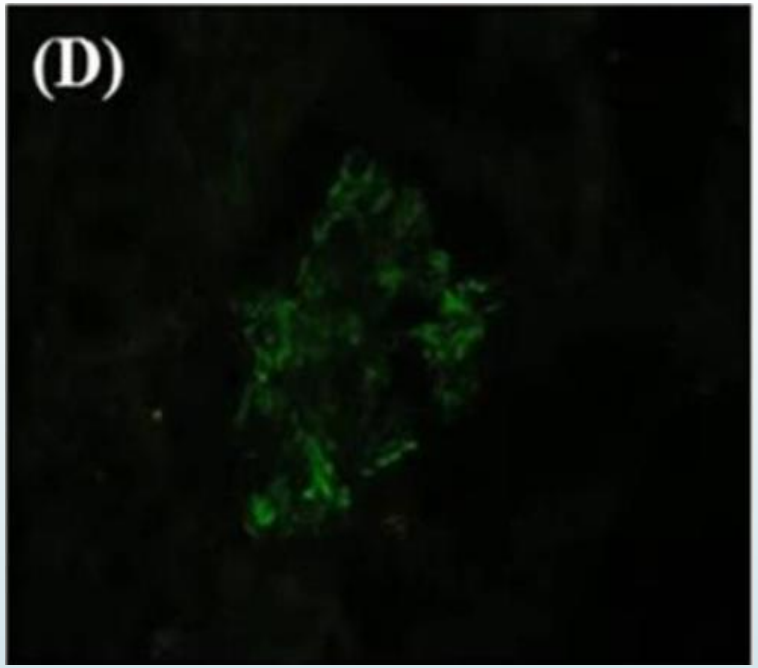
**Conclusion:** Our 3 case reports suggest that the disease severity of recurrent IgAN with endocapillary proliferation regardless of crescent formation can be minimized by the 4 doses of monthly rituximab regimen.

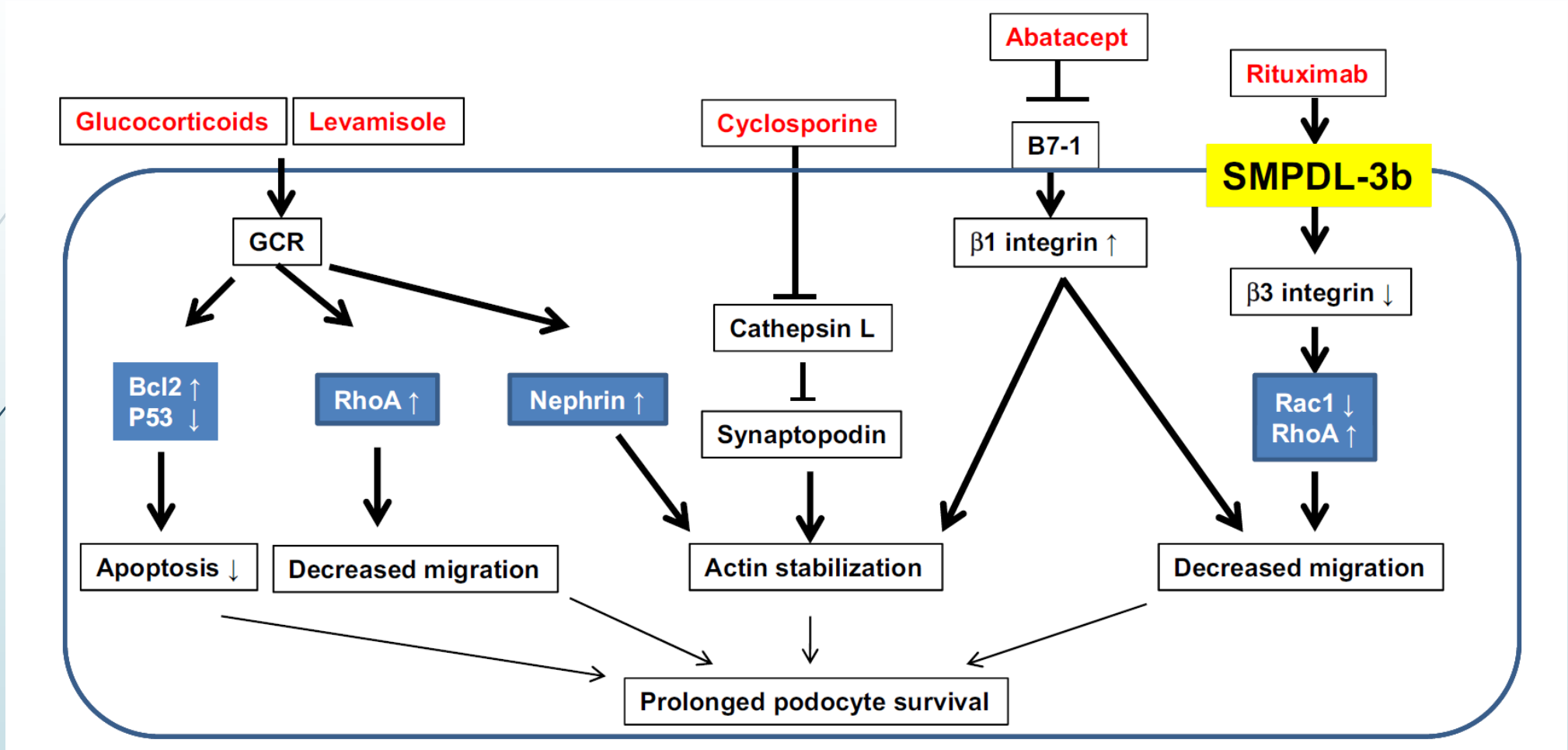

Autoimmune dysregulation increases production of antiglycan Ab
RTX
B cell
B cell
IgA1 producing B cell
IgA1-Ab complex
Mesangial cell
C1q
CD20
MAC
B cell
1
2
NK
B cell
APOPTOSIS
3
B cell
Macrophage
4

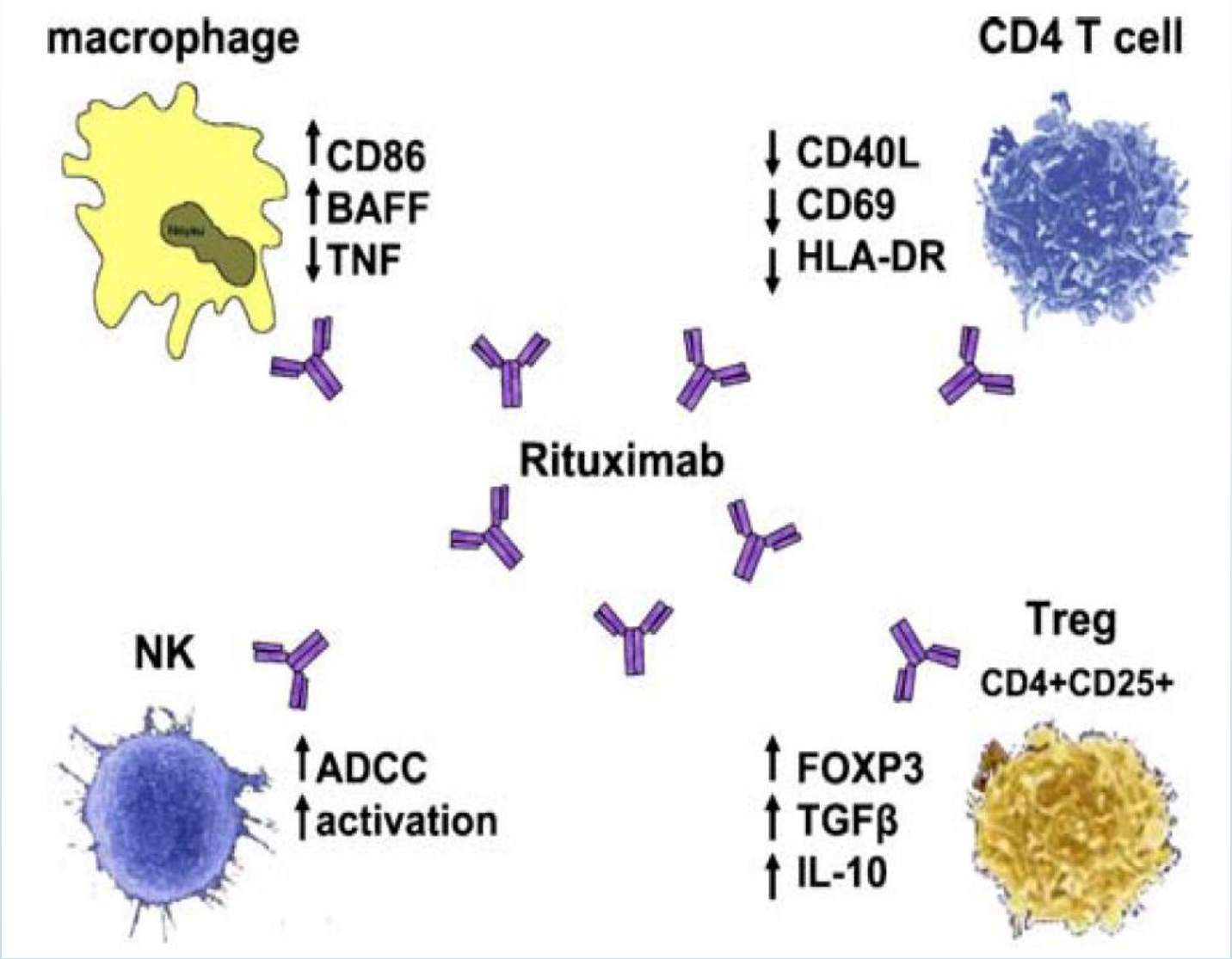
## Before treatment

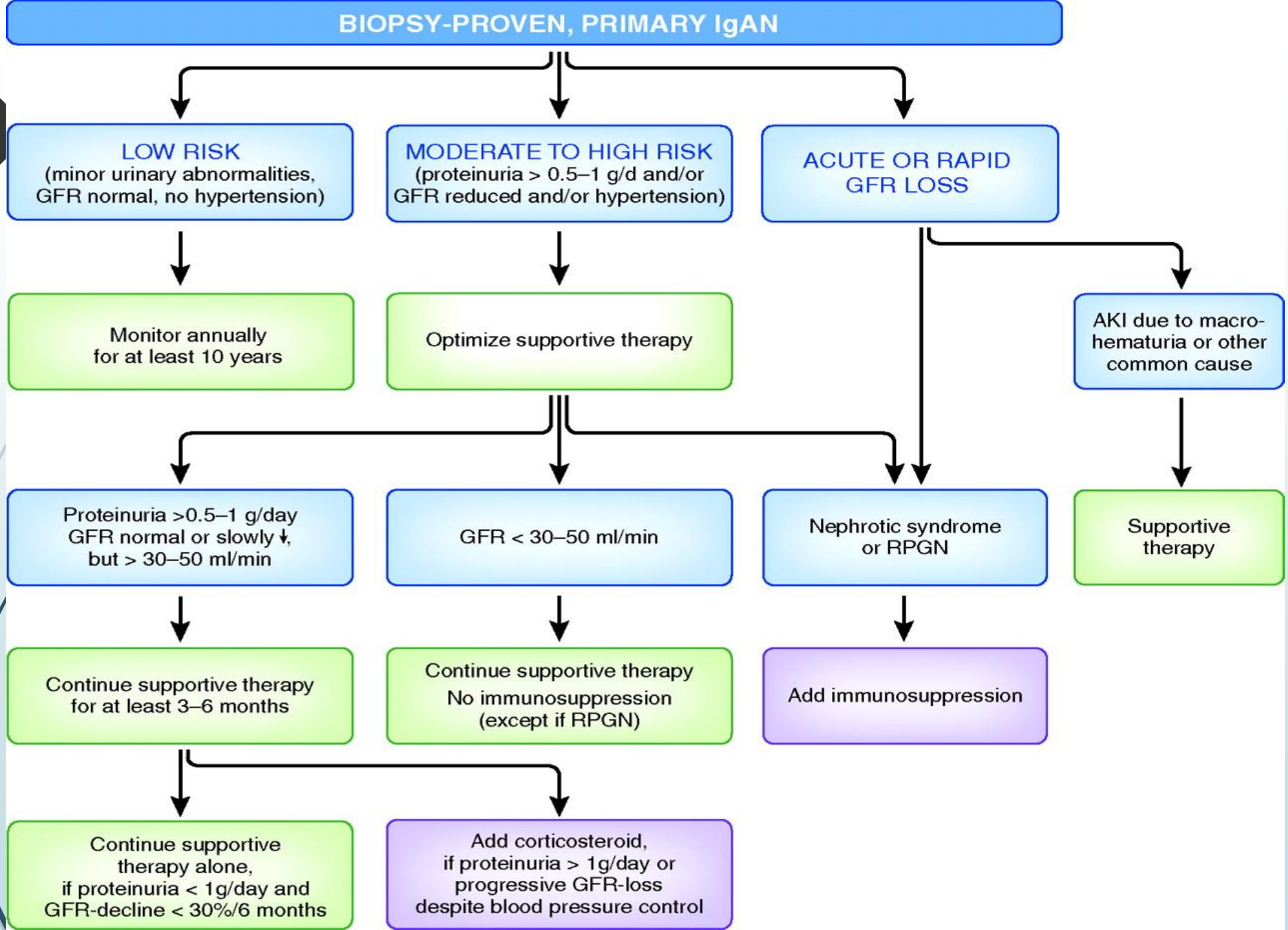



## After treatment




Glucocorticoids
Levamisole
Cyclosporine
Abatacept
Rituximab
B7-1
SMPDL-3b
GCR
β1 integrin ↑
β3 integrin ↓
Cathepsin L
Bcl2 ↑
P53 ↓
RhoA ↑
Nephrin ↑
Synaptopodin
Rac1 ↓
RhoA ↑
Apoptosis ↓
Decreased migration
Actin stabilization
Decreased migration
Prolonged podocyte survival


macrophage
CD4 T cell
↑CD86
↑BAFF
↓TNF
↓ CD40L
↓ CD69
↓ HLA-DR
Rituximab
NK
Treg
CD4+CD25+
↑ADCC
↑activation
↑ FOXP3
↑ TGFβ
↑ IL-10


BIOPSY-PROVEN, PRIMARY IgAN
LOW RISK
(minor urinary abnormalities, GFR normal, no hypertension)
MODERATE TO HIGH RISK
(proteinuria > 0.5–1 g/d and/or GFR reduced and/or hypertension)
ACUTE OR RAPID GFR LOSS
Monitor annually for at least 10 years
Optimize supportive therapy
AKI due to macro-hematuria or other common cause
Proteinuria >0.5–1 g/day GFR normal or slowly ↓, but > 30–50 ml/min
GFR < 30–50 ml/min
Nephrotic syndrome or RPGN
Supportive therapy
Continue supportive therapy for at least 3–6 months
Continue supportive therapy
No immunosuppression (except if RPGN)
Add immunosuppression
Continue supportive therapy alone, if proteinuria < 1g/day and GFR-decline < 30%/6 months
Add corticosteroid, if proteinuria > 1g/day or progressive GFR-loss despite blood pressure control