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RESEARCH ARTICLE

Disease-Specific Treatment for Primary Membranous Nephropathy: The Role of Monoclonal Antibodies

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ABSTRACT

Primary Membranous Nephropathy is an autoimmune disease caused by the deposition of Immunoglobulin G and complement components on the subepithelial layer of the glomerular capillary wall. It affects 5-10 patients per million population and is the second cause of nephrotic syndrome in adults after diabetic kidney disease. For decades steroids and non-specific immunosuppressive medications have been advocated as a therapeutic option for patients with membranous nephropathy at increased risk of kidney failure because of persistent nephrotic syndrome. These medications, however, have major and potentially fatal adverse effects that offset their potential benefits and should be abandoned. The discovery of nephritogenic autoantibodies against podocyte M-type phospholipase A2 receptor (PLA_2R) and thrombospondin type-1 domain-containing protein 7A (THSD7A) antigens provided a clear pathophysiological rationale for interventions specifically targeting B cell lineages to prevent antibody production and subepithelial deposition. The first-in-class anti-CD20 monoclonal antibody rituximab is safe and achieves remission in approximately two-thirds of patients with nephrotic membranous nephropathy. In PLA_2R-related disease, remission is invariably preceded by depletion of anti PLA_2R autoantibodies and relapse by their re-emergence into the circulation. Because of its superior risk/benefit profile as compared to non-specific immunosuppressive therapy, rituximab is now first-line therapy for patients with membranous nephropathy at risk of kidney failure. Novel monoclonal antibodies targeting CD20 cells (such as ofatumumab and obinutuzumab) and their differentiation (belimumab) or targeting long-living antibody producing CD38 memory cells (daratumumab, felzartamab) along with proteasome inhibitors such as bortezomib are being evaluated for the treatment of nephrotic patients with membranous nephropathy who are resistant or intolerant to rituximab. Complement inhibitor therapy might serve to stop the glomerular inflammatory process until the benefits of these medications become effective.

Thus, major advances in the understanding of the mechanisms of membranous nephropathy have led to novel treatment perspectives. The integrated evaluation of serum autoantibody titer and proteinuria, together with serum albumin levels in patients with overt nephrotic syndrome, could guide diagnosis of membranous nephropathy and individually tailored treatment protocols. The introduction of monoclonal antibodies targeting disease-specific mechanisms will pave the way for a novel therapeutic paradigm based on the principle of precision medicine and personalized therapy.

Keywords: membranous nephropathy, nephrotic syndrome, monoclonal antibodies, CD20, CD38, PLA_2R, rituximab, ofatumumab, obinutuzumab, felzartamab, belimubab, complement

INTRODUCTION

Primary Membranous Nephropathy (PMN) is an autoimmune disease caused by the deposition of Immunoglobulin G and complement components on the subepithelial layer of the glomerular capillary wall. It affects five to ten patients per million population and is the leading cause of nephrotic syndrome (NS) in adults after diabetic kidney disease[1,2]. Patients with PMN and non-nephrotic proteinuria (<3.5 g per 24 h) have a good prognosis with a supportive therapy based on optimized inhibition of the Renin-Angiotensin-System with Angiotensin-Converting-Enzyme inhibitors (ACEi) and/or Angiotensin-Receptor-Blockers (ARBs)[3–6]. Without immunosuppression, however, approximately one-third of patients with PMN and NS (proteinuria >3.5 g per 24 h and/or hypoalbuminemia) progress to end stage kidney disease (ESKD)[7, 8].

Steroids and non-specific immunosuppressive medications may achieve remission of the NS more effectively than placebo and supportive therapy but are associated with serious and potentially fatal complications that may offset the potential benefits of therapy[3]. Thus, the 2012 Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommended that the use of non-specific immunosuppressive therapy should be restricted to patients with persistent NS[10] because, in this context, the reduced risk of ESKD could offset the risks of serious adverse events.

Mechanisms of Disease

Membranous nephropathy was first described as a specific disease entity in 1957 by David Jones[9]. In 1959, the finding that rats injected with an extract of proximal tubular cells induced the deposition of subepithelial immune complexes that were similar to those observed in humans with PMN, strongly suggested the possibility of an immune-mediated pathogenesis of the disease[10]. These immunocomplexes, however, contained IgG antibodies targeting megalin, a protein expressed on both rat tubuli and podocytes[11], but not on human podocytes. A target antigen in humans was first identified in 2002 in the baby of a woman with a neutral endopeptidase (NEP) deficiency[12]. Finding that anti-NEP alloantibodies produced by the mother crossed the placenta and bound to NEP expressed on fetal podocytes[12] confirmed the role of autoantibodies in the pathogenesis of PMN in humans. In 2009, circulating autoantibodies against the secretory phospholipase A_2 receptor (PLA_2R), primarily of the IgG4 subclass, were detected in ~70% of patients with PMN[13]. Antibodies were disease-specific as they could not be found in patients with other proteinuric nephropathies[13], but were associated with PMN in several cohorts of patients of different ethnicities[14,15]. The pathogenic role of the PLA_2R antigen was confirmed by the significant association found between single nucleotide polymorphisms in the PLA_2R gene and the development of the disease[16]. Circulating autoantibodies against another human podocyte antigen - the thrombospondin type 1 domain containing 7A protein (THSD7A) - have been subsequently observed in 5–10% of patients with PMN who do not have circulating antiPLA_2R autoantibodies[17]. The finding that most PMN patients have an autoimmune response against either PLA_2R or THSD7A, but very rarely against both[18], suggests that both antigens can be the primary target of specific autoimmunity and confirms that PLA_2R-associated and THSD7A-associated PMN are separate disease entities[2]. In the following years, a number of proteins, such as exostosin 1 and 2, protein kinase C-binding protein neural epidermal growth factor-like 1(NELL-1), serine protease high temperature requirement A 1 (HTRA-1), semaphorin 3B, protocadherin 7, neutral cell adhesion molecule 1, transforming growth factor-β receptor 3, contactin 1, neutrin G1 and protocadherin Fat-1 have been reported as additional potential autoantigens in PMN. These findings might enable the characterization of different PMN subpopulations and elucidate the mechanisms underlying disease initiation[19].

The predictive role of Anti-PLA_2R antibody titer

Anti-PLA_2R antibody titer correlates with disease activity and patient outcome[14,20–27]. Low autoantibody levels at diagnosis predict spontaneous remission[28,29], whereas high baseline anti-PLA_2R antibody levels correlate with a reduced probability of spontaneous remission[28], are associated with progression to NS in patients with initial non-nephrotic proteinuria[26], and predict a high risk of relapse and progressive loss of kidney function[25,26,30]. Moreover, decreasing anti-PLA_2R antibody levels strongly predicts remission of proteinuria[14,24,31] and response to various traditional and novel immunosuppressive treatments[24,27]. **(Figure 1, Panel A).** Response to treatment was similar in patients with or without detectable antibodies or without antibody data[27] **(Figure 1, Panel B).** Conceivably, in PLA_2R-negative disease, PMN can be sustained by other nephritogenic autoantibodies such as anti-THSD7A antibodies that, similarly to anti-PLA_2R antibodies, have been reported to predict disease activity

and response to therapy[17,32] Whether progression and response to treatment of patients with PMN can be affected not only by the overall titer of circulating anti-PLA$_2$R autoantibodies, but also by their nature is matter of a lively debate[19,33,34].

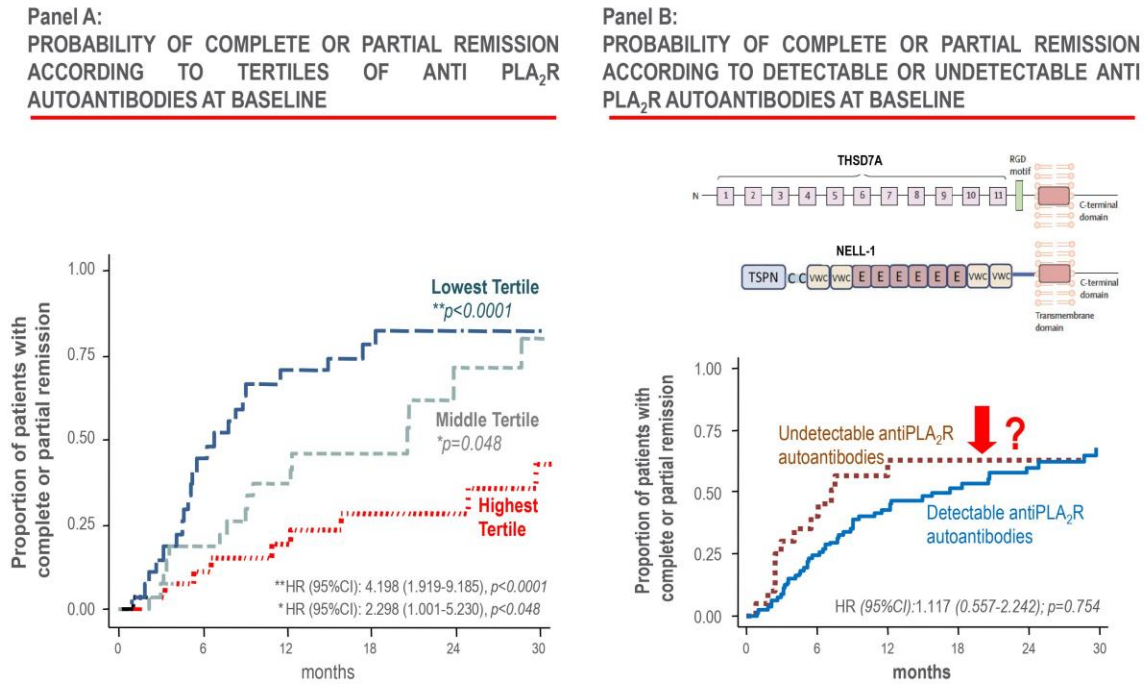

Figure 1. Kaplan-Meier curves for the proportion of patients with PMN who achieved the combined end point according to anti PLA2R antibodies at baseline[27].
Panel A. Probability of complete or partial remission according to tertiles of PLA2R antibodies at baseline. The probability of achieving the combined endpoint progressively decreased from the lowest to the middle and the highest tertile (reference). The upper and lower HRs refer to lowest and middle tertiles versus highest tertile (reference). **Panel B.** Probability of complete or partial remission according to detectable or undetectable anti PLA2R antibodies at baseline. The probability of achieving the combined endpoint was similar in the two groups. In the subgroup with undetectable anti PLA2R antibodies at baseline, other auto antibodies could be involved such as anti THSD7A or anti NELL-1 antibodies. 95% CI, 95% Confidence interval; HR, Hazard Ratio.

Toward a disease-specific therapeutic approach
After almost 40 years of empirical treatment, the discovery of anti-PLA$_2$R and anti-THSD7A autoantibodies provided the first clear pathophysiological rationale for interventions specifically aimed at preventing antibody production **(Figure 2)** or their binding to specific antigens with subepithelial deposition of antibody–antigen immunocomplexes **(Figure 3).** Such treatments can prevent complement activation and podocyte damage, eliminate NS, and even resolve the glomerular pathology of MN[35,36]. Thus, combined assessment of circulating anti-PLA$_2$R or anti-THSD7A autoantibodies and proteinuria, and serum albumin level in patients with hypoalbuminemia, could help monitoring disease activity and guiding personalized therapy with conventional immunosuppressive protocols or specific B-cell targeting monoclonal antibodies[37]. Persistent proteinuria in the face of low antibody levels might reflect chronic damage, whereas high antibody levels in the absence of clinical symptoms could signal an impending relapse[37]. In antibody-negative patients, proteinuria and serum albumin levels remain the most sensitive markers of disease severity and outcome.

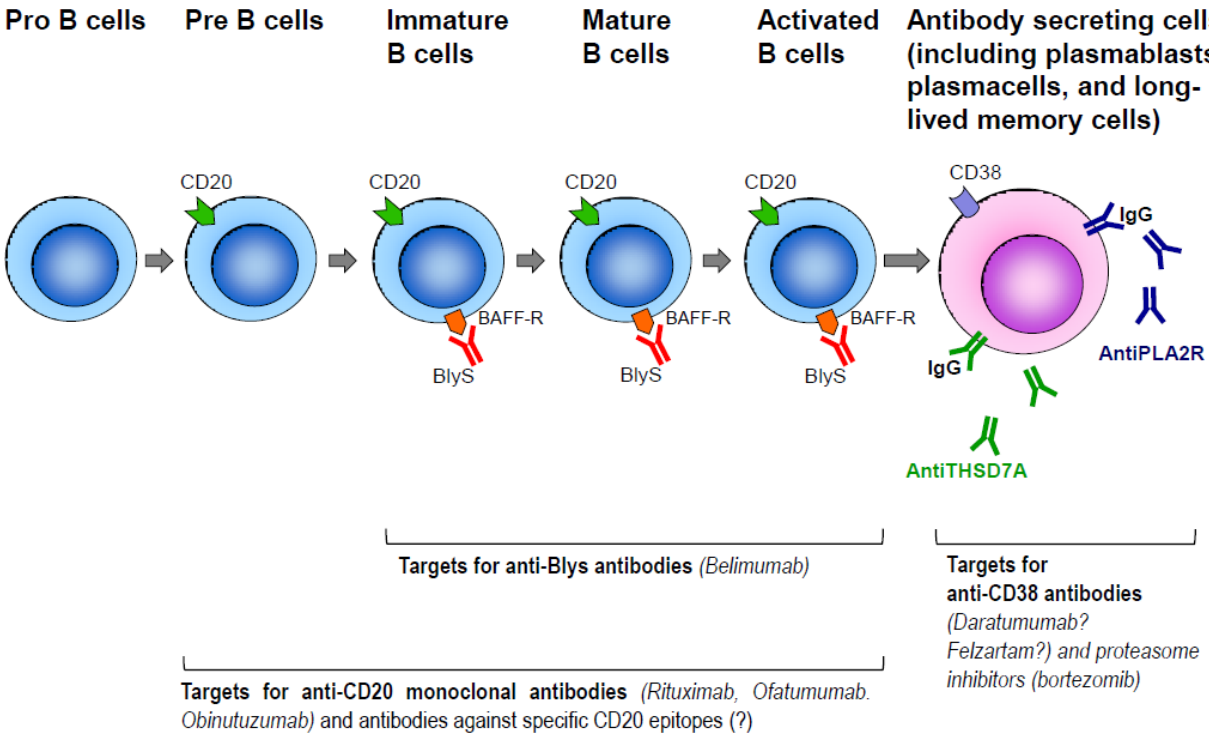

Figure 2. Targets for anti CD20 monoclonal antibodies in B cell lineages.
B cells emerge from bone marrow stem cells as pro-B cells and mature into pre-B cells, immature B cells, mature B cells, and, activated B cells. Eventually, they develop into antibody-secreting cells, including plasmablasts, plasma cells, and long-lived memory plasma cells that secrete IgA, IgE, IgG, and IgM antibodies. Autoreactive B cell clones can produce anti-PLA_2R and anti-THSD7A antibodies and, conceivably, autoantibodies against unknown antigens expressed on podocyte cells. As B cells mature, they develop various markers on the cell surface that can become targets for specific monoclonal antibodies. Anti-CD20 monoclonal antibodies, such as rituximab and ofatumumab, bind and kill CD20 expressing B cells (pre-B cells, and immature, mature, and activated B cells), but not plasmablasts, mature plasma cells or memory plasma cells as they do not express this antigen. Plasma cells express CD38 and might, therefore, be a target for anti-CD38 antibodies such as daratumumab, felzartamab or isatuximab. Immature, mature, and activated B cells express receptors for the B lymphocyte stimulator (BLyS) such as B cell activating factor receptor (BAFF-R), B cell maturation antigen (BCMA), and the transmembrane activator and CAML (calcium-modulating cyclophilin ligand) interactor (TACI). The anti-BLyS monoclonal antibody belimumab might, therefore, prevent B cell differentiation into plasma cells by blocking the interaction between this lymphocyte stimulator and its receptors. Proteasome inhibitors, such as bortezomib, can prevent antibody production by inducing plasma cell apoptosis, whereas anti-CD38 monoclonal antibodies, such as daratumumab, felzartamab and isatuximab, can directly induce plasma cell cytolysis.

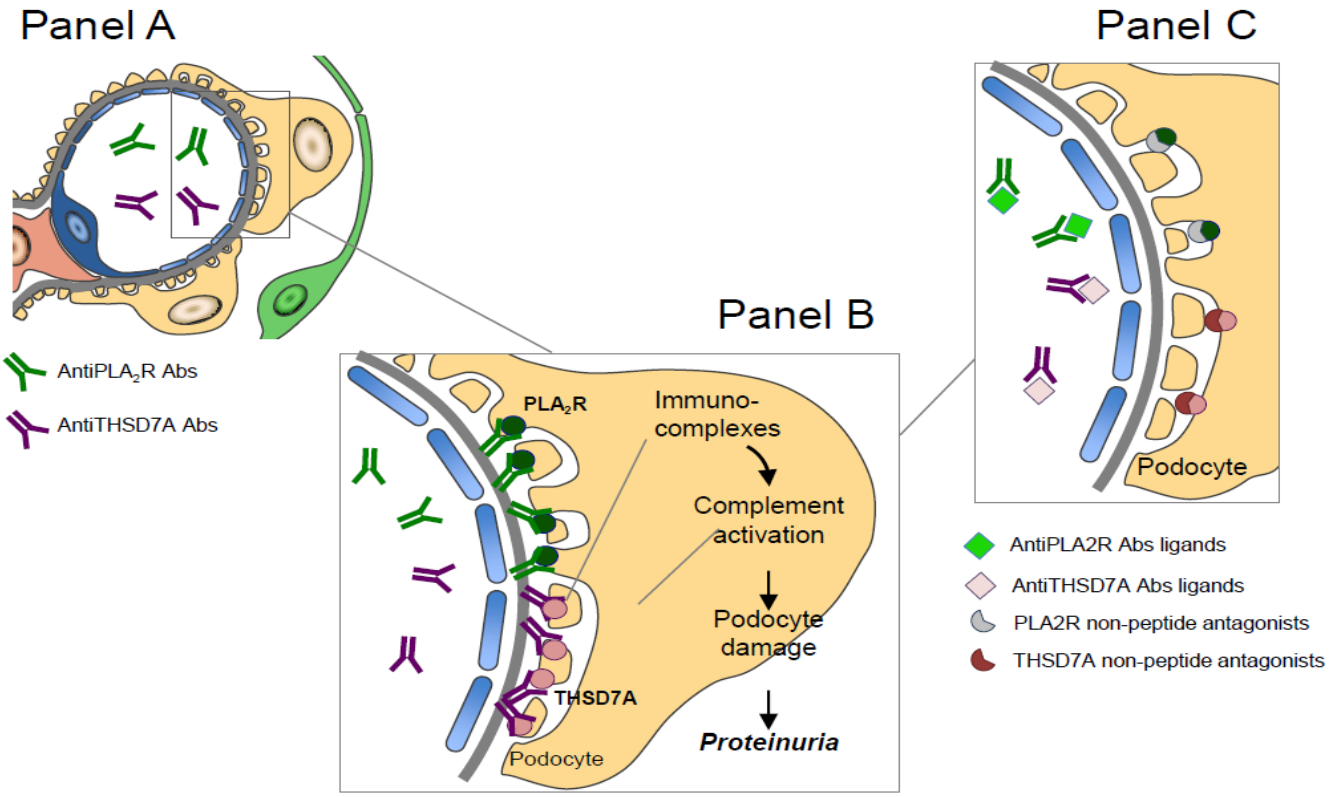

Figure 3. Prevention of antigen–antibody immunocomplex deposition on the glomerular basement membrane.

Panel A. A glomerular capillary and its basement membrane surrounded by podocytes. Anti PLA_2R and anti THSD7A antibodies are shown in the capillary lumen. **Panel B.** Binding of circulating anti PLA_2R and anti THSD7A autoantibodies to their specific PLA_2R and THSD7A receptors on the podocyte cell surface. Antigen-antibody binding results into the deposition of antigen–antibody subepithelial immunocomplexes that activate the complement system with secondary podocyte damage, sieving dysfunction, and proteinuria. **Panel C.** In theory, antibody-antigen binding and subepithelial immunocomplexes deposition could be prevented by specific ligands that bind circulating antiPLA_2R and THSD7A antibodies or interact with their specific PLA_2R and THSD7A receptors on the podocyte cell surface thus preventing antigen-antibody binding and consequent deposition of antigen–antibody subepithelial immunocomplexes.

Targeting autoreactive B-cell clones producing nephritogenic autoantibodies: The role of anti-CD20 monoclonal antibodies

Availability of an anti CD20 monoclonal antibody[38] allowed investigation into whether targeted B-cell depletion, with inhibition of nephritogenic autoantibody production, improves the outcome of patients with PMN while avoiding the adverse effects of steroids and immunosuppressants. B cells originate from hematopoietic stem-cell precursors in the bone marrow and sequentially develop into pro-B cells, pre-B cells, immature B cells, and mature B cells. Immature B cells undergo clonal deletion or rearrange immunoglobulin gene segments before entry into the transitional B-cell pool. In the spleen, transitional B cells depend on B cell–activating factor for survival and to differentiate into mature B cells. Mature B cells are activated by foreign antigens and enter germinal center reactions to generate isotype-switched memory B cells and plasma cells[39] **(Figure 2).**

Pre B cells, immature B cells, mature B cells and activated B cells all express the CD20 antigen on their surface and are therefore potential targets for anti CD20 monoclonal antibodies **(Figure 2)** that may elicit actin-dependent, lysosomal cell death[40], antibody-dependent cellular cytotoxicity (ADCC), and complement-dependent cytotoxicity (CDC)[41]. ADCC is mediated by the interaction of the Fc region of anti-CD20 monoclonal antibodies with FcγRIIIa, that is expressed on natural killer cells and macrophages. FcγRIIIa is cross linked by binding to CD20 on target cells, stimulating effector cells to release lytic enzymes, with consequent B-cell death[41]. CDC activity is initiated by complement component C1q interaction with the anti-CD20 monoclonal antibody Fc region

exposed after binding to CD20 on the B-cell surface, with activation of the classical complement cascade, and insertion of the membrane attack complexes (MAC) into the cell membrane, with consequent cytolysis[42].

Type I CD20 monoclonal antibodies, such as rituximab and ofatumumab, have potent CDC[41], whereas type II antibodies, such as obinutuzumab, weakly bind C1q and have modest CDC activity[43] but more efficiently induce a non-apoptotic lysosomal form of cell death[44,45]. As compared to rituximab, second generation type 1 antibodies and type 2 anti CD20 monoclonal antibodies do not simultaneously bind to the large loop of the CD20 and to FcγRIIb and consequently are not sensitive to B-cell defense mechanisms such as CD20-antibody complex internalization[46,47]. This difference might explain the remarkably stronger B cell lytic effect of type II antibodies as compared to rituximb[48].

Rituximab: Seminal experience

Rituximab, the ancestor of anti CD20 monoclonal antibodies, is a chimeric monoclonal IgG1 that binds to the large loop of the CD20 antigen[49] **(Figure 4)**. CD20 binding results in increased calcium conductivity and induction of apoptosis[50] along with ADCC mediated by activation of effector cells, including granulocytes, natural killer cells and macrophages[51]. But the predominant cytolytic effect of Rituximab is mediated by CDC[52]. In addition, rituximab can exert a direct antiproteinuric effect by preserving glomerular expression of podocin and nephrin, which stabilizes the cytoskeleton via an apparent B-lymphocyte independent mechanism[53].

Largely before antiPLA$_2$R antibodies were identified as disease-specific nephritogenic autoantibodies, rituximab was tested in eight patients with PMN and long-term proteinuria[54]. Over 20-week follow-up proteinuria had decreased by 62% and serum albumin had increased by 31% versus baseline **(Figure 5)**. In two patients proteinuria decreased to < 1g/24-hours and in three additional patients to < 3.5 g/24-hours, and no SAEs occurred[54]. Reduction in proteinuria was sustained over 1 year and was associated with stable kidney function and a reduction in body weight, blood pressure, and serum cholesterol level[55].

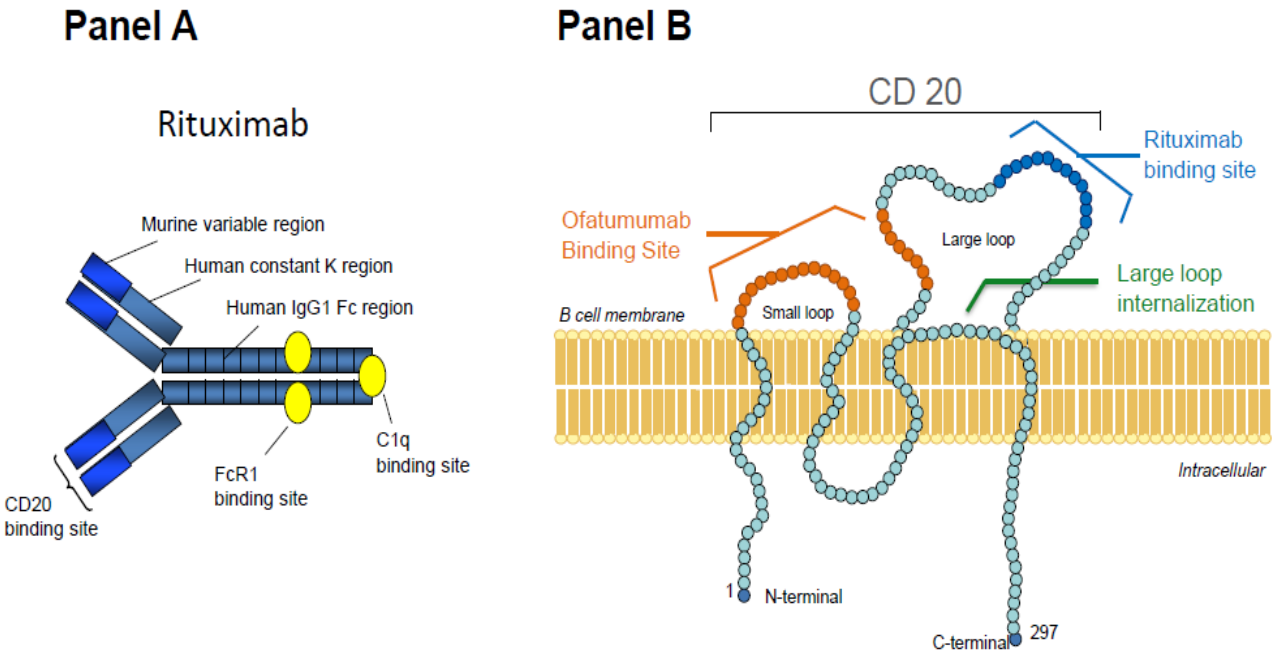

Figure 4. Rituximab and the CD20 antigen. Panel A. Rituximab Structure. Panel B. The CD 20 molecular configuration. CD20 is a tetra-transmembrane protein on the membrane of B cell with small and large extracellular loops. The binding sites of the CD20 monoclonal antibodies rituximab and ofatumumab are indicated in blue and orange, respectively. Rituximab binds an epitope on the large loop only, whereas ofatumumab specifically recognizes an epitope encompassing both the small and large extracellular loops of the CD20 molecule. A defense mechanism of the B cell is internalization of the large loop along with the binding site for rituximab. This results in B-cell resistance to rituximab. Large loop internalization does not result in resistance to ofatumumab, because ofatumumab binds also to the epitope on the CD20 small loop.

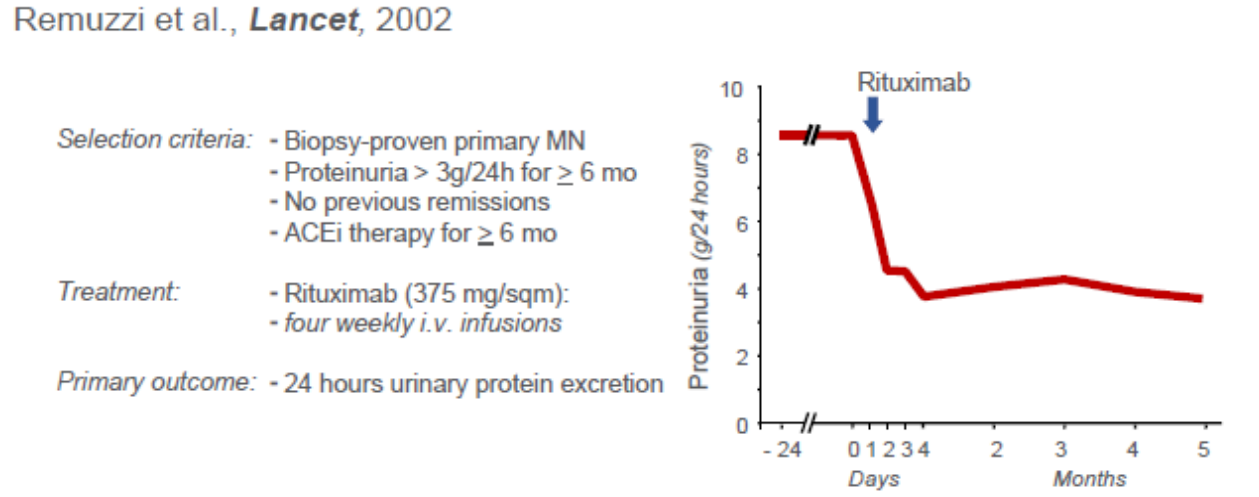

Figure 4. The first experience with anti CD20 monoclonal antibody therapy in PMN. Time course of 24-h urinary protein excretion rate in eight individual patients with PMN and more than six weeks of persistent NS despite optimized supportive therapy from 24 weeks before Rituximab administration (week 0) up to five months of follow up[54]

Rituximab: Expanding evidence

Among 35 patients with PMN, that in approximately half of cases had failed previous immunosuppressant therapy, two 1 g infusions 2 weeks apart, or four once-weekly infusions of 375 mg/m^2 of rituximab, achieved complete or partial remission of proteinuria in 50% and 80% of patients at 1 and at 2 years, respectively[56,57]. The reduction in proteinuria was similar with the two dosing regimens and was gradual and sustained over time. The recovery of B-cell counts after treatment was completed, however, was faster than in patients without proteinuria treated with rituximab, such as those with rheumatoid arthritis, or non-Hodgkin lymphoma, or vasculitis associated with antineutrophil cytoplasmic antibody (ANCA)[56–59]. This finding could be explained by rituximab shortened half-life because of drug urinary loss in patients with severe proteinuria. However, rituximab levels did not correlate with treatment response[56,57]. Thus, whether the dose of rituximab should be adjusted according to the severity of proteinuria remains uncertain.

B-cell depletion led to complete or partial remission of NS in 65% of 100 consecutive patients with PMN, and additional 20 patients experienced a >50% reduction in proteinuria[60]. The median duration of proteinuria before rituximab administration was >2 years (approximately 6 years in those previously exposed to other immunosuppressive regimens) and all patients had been taking ACE inhibitors or ARBs for at least 6 months. Therefore, NS remission was unlikely spontaneous. At the 4-year follow up, all patients had achieved complete or partial remission[60]. However, proteinuria reduction was a progressive, time-dependent effect with the nadir of median 24-hour urinary protein excretion being achieved at least at 24 months after rituximab infusion[60] **(Figure 5).** Thus, adequate patient follow-up is needed before any conclusion on the response to rituximab is drawn, in clinics as well as in research. Finding that anti-PLA$_2$R antibody depletion preceded NS remission[21,27], and that antibody re-emergence into the circulation preceded disease recurrence[27], provides convincing evidence of a causal relationship between anti-PLA$_2$R antibody production/depletion and disease activity/remission. Finding that reduction in proteinuria up to the point of complete remission follows B-cell depletion by several months is consistent with evidence that after progressive reabsorption of *in situ* immune deposits, extensive immunologic damage requires prolonged podocyte remodeling before the architecture and function of the glomerular filtration barrier are restored, as observed after transplantation of kidneys from rats with experimental MN (Heymann nephritis) into syngeneic rats without the disease[61].

A meta-analysis of 21 trials demonstrated that rituximab achieved remission as second-line therapy as effectively as in patients without previous immunosuppression[62]. Clinical benefits were associated with regression of the histological lesions characteristic of PMN, along with decreased glomerular IgG4 and C3 staining **(Figure 6)**, reabsorption of electron-dense subepithelial deposits **(Figure 7)**, an increased number of podocyte slit diaphragms, and an increased percentage of electron-dense slit diaphragms that correlated with treatment-induced decrease in albumin fractional clearance[35]. Reduction in electron-dense immune deposits was never observed after cyclosporine therapy[63].

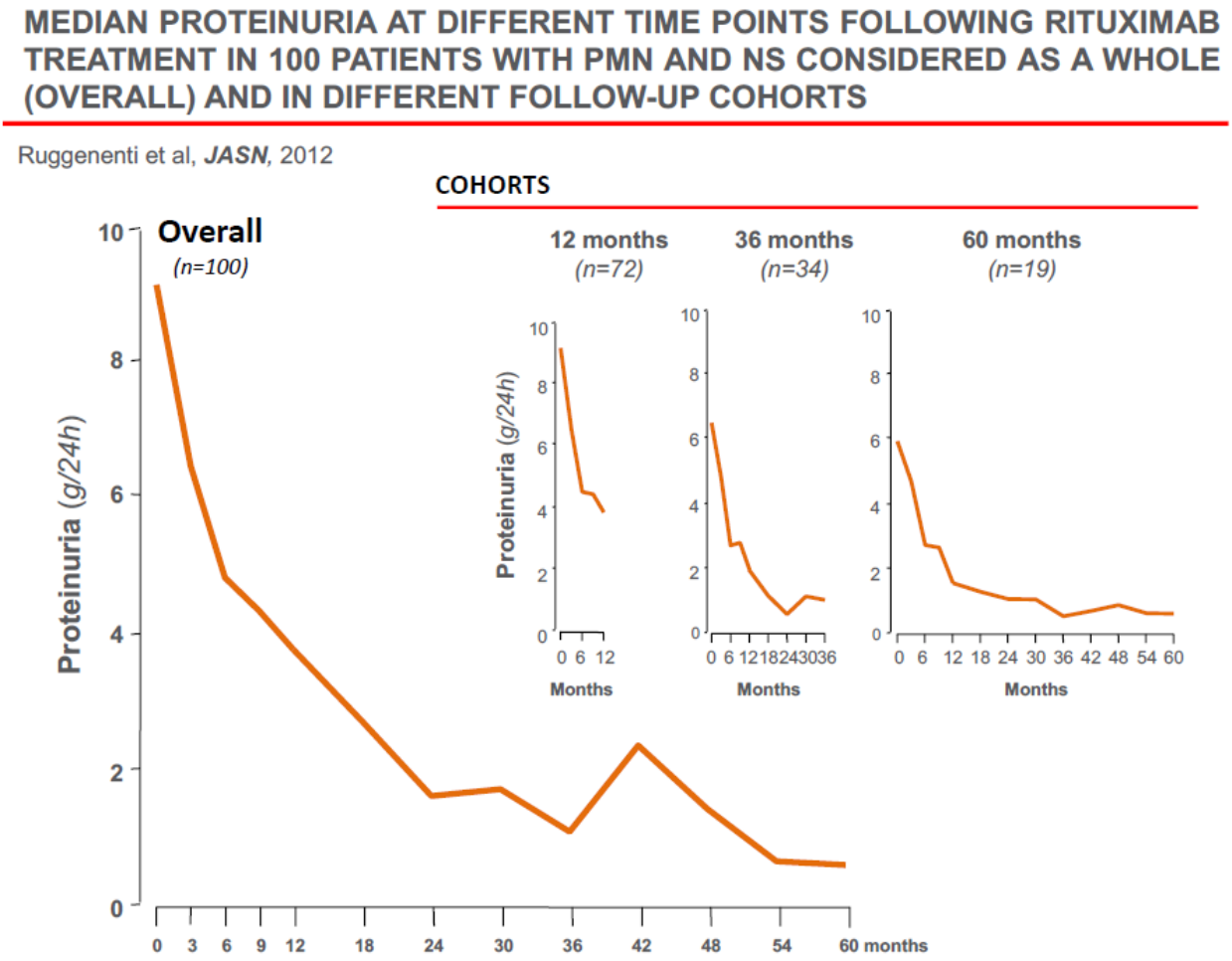

Figure 5. Median 24-hour proteinuria at different time points after rituximab infusion in 100 patients with PMN and NS considered as a whole (Overall) and in three cohorts of patients with a follow-up of 12, 36 and 60 months, separately. Proteinuria reduction is a time-dependent effect and the nadir value of proteinuria is observed at least 24 months after rituximab infusion

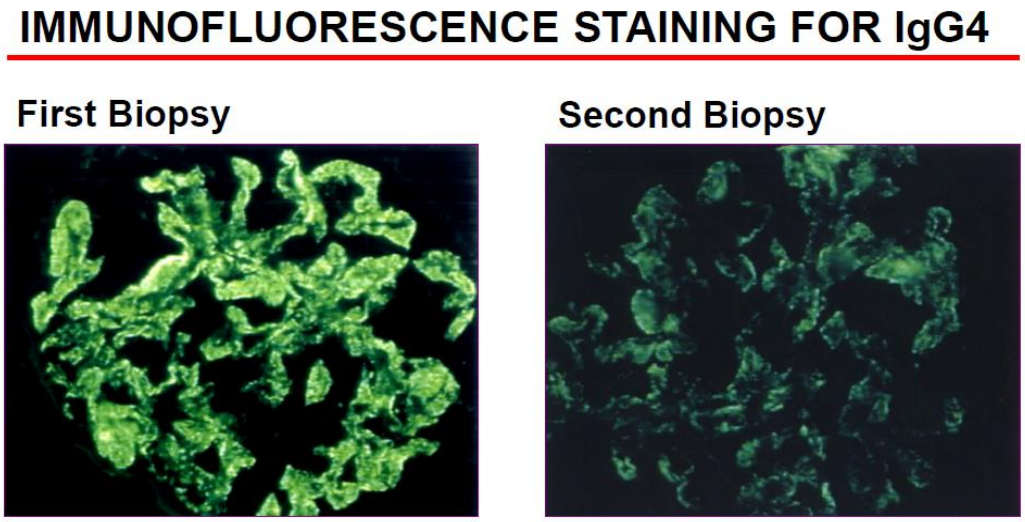

Figure 6. IgG4 immunostaining in a kidney histology sample taken from a representative patient with PMN before Rituximab administration (First biopsy, Left Panel) and after progression to complete remission of the NS (Second biopsy, Right Panel)[35]. The diffuse, granular immunostaining for IgG4 along glomerular capillary walls observed at first biopsy (Left Panel) was not detectable any longer at repeat biopsy (Right Panel).

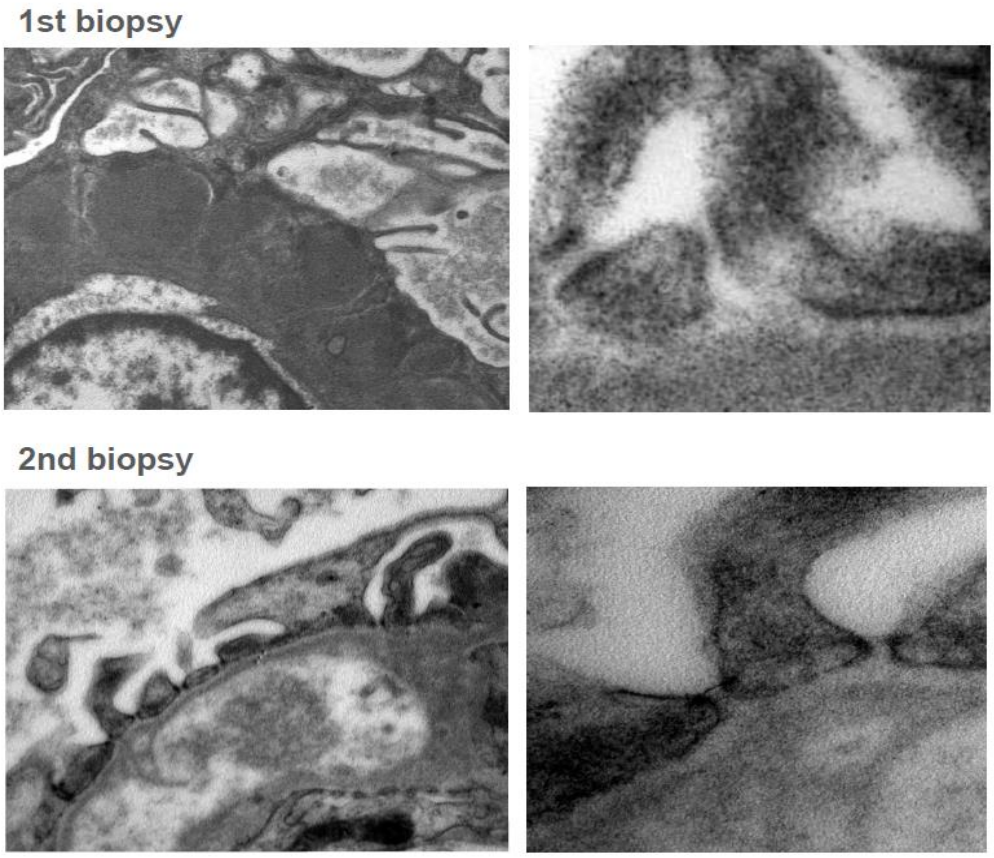

Figure 7. Representative transmission electron micrographs of the capillary wall in a representative patient before (First biopsy) and after (Second biopsy) rituximab therapy[35]. The diffuse subepithelial electron-dense immune deposits observed at baseline (Upper left panel) almost completely disappeared after rituximab therapy (Lower left panel). Before rituximab therapy, a high percentage of slit pores did not show intact diaphragm ultrastructure between neighboring podocytes (Upper right panel), whereas the electron-dense filamentous images were instead detectable after treatment (Lower right panel). Original magnification: Left panels, x18,000; Right panels, x56,000.

The overall safety profile of rituximab

In five randomized controlled trials[64–68], the average incidence of severe infections in patients treated with rituximab (10%) was comparable to that observed in patients receiving placebo (12%). A total of 57 patients with progressive multifocal leukoencephalopathy (PML) was identified from 1997 to December 2008 among rituximab-treated patients by clinicians from 12 cancer centers or academic hospitals, or by reviewing reports of the Food and Drug Administration (FDA), the manufacture's database and publications[69]: 52 had lymphoproliferative disorders and 5 autoimmune diseases. All of them had been previously exposed to corticosteroids and several antineoplastic agents, including cyclophosphamide in 74% and chlorambucil in 21% of cases, in different and multiple combinations. Consistently PML, pneumocystis pneumonia, and pulmonary fibrosis that have been ascribed to rituximab[70] were observed in patients with lymphoproliferative[113] or autoimmune diseases[71], or those who had undergone bone marrow transplantation[72], all of whom had been exposed to other immunosuppressant drugs. No one had received rituximab as the only immunosuppressive medication. Thus, no event was causally related to rituximab[69], whereas more than 30 cases of PML have been described in patients with vasculitis who were treated with cyclophosphamide-based regimes[73,74]. In a child with steroid-dependent idiopathic NS, exposure to other immunosuppressant drugs was likely the cause of fulminant enterovirus myocarditis requiring heart transplantation 13 months after rituximab therapy[75]. In fact, finding that replication of John Cunningham virus and BK virus is not affected by rituximab[76] indicates that, unlike conventional immunosuppressants, rituximab does not increase the risk of viral reactivations. Consistently, in children with frequently relapsing NS, the incidence of infections with rituximab or placebo was similar[77]. Actually, the risk of infections and other complications is reduced when rituximab is used to aid withdrawal from steroids and other immunosuppressants[78].

The only adverse effects that can be ascribed with certainty to rituximab are infusion-related events such as hypotension, cutaneous rash, and bronchial wheezing[60] that usually are not serious and resolve with temporary interruption of the infusion and/or hydrocortisone[60]. Premedication with 10 mg of chlorphenamine and 500 mg of hydrocortisone minimizes the risk of these events. SAEs occurring after exposure to rituximab are rare. Finding that in 100 patients treated with rituximab SAEs clustered in those who did not achieve remission strongly suggests that these events were related to the underlying disease rather than to treatment[36]. The rate of infections and cardiovascular events was actually reduced in patients who achieved remission[60].

The risk of serious adverse events (SAEs), such as malignancies, that occur as late as 10–20 years after immunosuppressive treatment[79] and, therefore, are not captured during the observation period, cannot be excluded from trials of steroids and alkylating agents[80–82]. However, data from patients receiving lifelong rituximab therapy for chronic lymphomas, or those exposed to high cumulative doses for the treatment of autoimmune diseases or lymphoproliferative disorders over a period exceeding ten years, show that rituximab is safer than other immunosuppressants[83–85]. In a large cohort of patients with rheumatoid arthritis who were followed up for 11 years, rituximab was not associated with an increased risk of cancer[86]. The three malignancies observed over a median of 29 months in 100 consecutive patients with PMN treated with rituximab[60] is likely to reflect the age-adjusted incidence of cancer in the general population[87]. Notably, the patient who eventually died of lung cancer had been previously treated with steroids and alkylating agents.

Hypogammaglobulinemia has been reported during repeat cycles of rituximab[88], in particular when it was administered in combination with other immunosuppressants, such as mycophenolate mofetil[89]. This adverse effect has been associated with excess risk of infections[90,91], but not in patients with PMN[56,60,92,93]. Notably, hypogammaglobulinemia is a major complication of NS that may recover with rituximab-induced remission of the NS.

Comparative risk/benefit profile of rituximab and non-specific immunosuppressive therapy in PMN

Retrospectively comparative analyses between two well-defined cohorts of PMN patients with persistent NS - 100 treated with rituximab and 103 with a steroid and cyclophosphamide (St-Cp) combination regimen - who had been monitored according to predefined standardized protocols[60,94] at two different nephrology units in Europe[92] showed that over a median follow-up of 40 months, the rituximab group had significantly fewer serious and non-serious adverse events than the St-Cp group **(Figure 8)**. Although the cumulative incidence of partial remissions was lower in the rituximab group, rates of complete remission and the composite renal end point (doubling of serum creatinine vs baseline, ESKD or death from any cause) did not differ significantly

between groups. However, the rate of serious and even fatal adverse events was more than fourfold higher in the St-Cp group than in the rituximab group **(Tables 1 and Table 2).** Moreover, 83% of the SAEs observed in the St-Cp group were likely or possibly treatment-related, whereas all the SAEs observed in the rituximab group were unrelated to treatment. Six cases of cyclophosphamide-related myelotoxicity occurred in addition to ten cases of hyperglycemia along with seven thromboembolic events and one case of osteonecrosis which were conceivably related to concomitant steroid therapy[92]. The rate of infections in the rituximab group was similar to that in the general population and were unlikely to be related to treatment, whereas infections in steroid and cyclophosphamide-treated patients were more likely to be severe and to result in hospital admission (11 serious infections, including three fatal cases of sepsis, in addition to 37 nonserious infections). Moreover, three blood malignancies and five solid tumors (fatal in two patients) were observed in the St-Cp group and were most likely related to treatment. One cancer was thought likely to be related to exposure to chlorambucil several years earlier. Thus, St-Cp combined therapy in PMN confers a threefold increase in the risk of cancer compared with the general population, which translates into an annual risk increase of 0.3–1.0%[95]. Taken together, these findings support the well-established carcinogenic effects of alkylating agents[95,96].

Notably, the adverse events associated with rituximab in studies reported from 2002[54] to now are less frequent and less severe even as compared to those (most likely) under-reported with the combination of steroids and cyclophosphamide, or cyclosporine when safety data were obtained from non-monitored trials conducted before the Guideline for Good Clinical Practice E6(R1) was published in 1996[97].

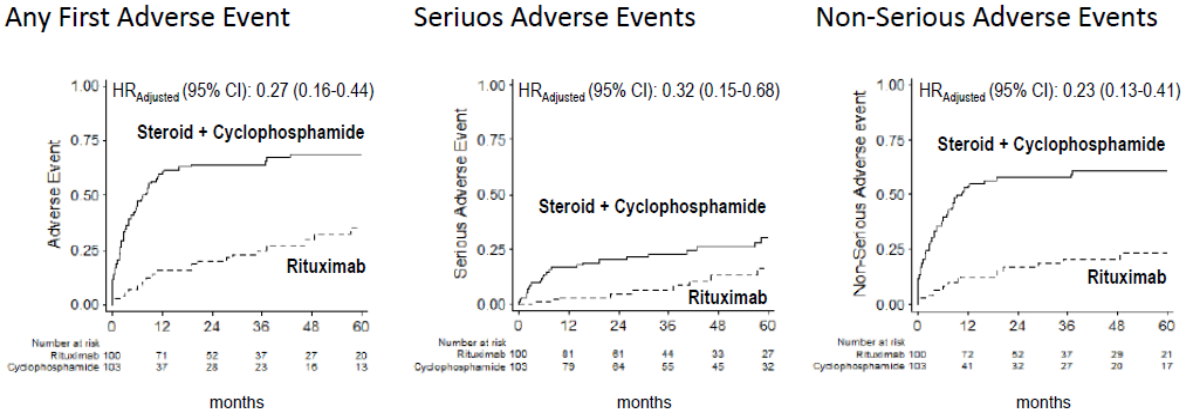

Figure 8. Cumulative incidence curves for time until the first adverse event, either serious or non-serious (Left Panel), to the first serious adverse event (Middle Panel) or to the first non-serious adverse event (Right Panel). The solid lines describe the events in steroid and cyclophosphamide-treated patients; the dashed lines the events in rituximab-treated patients

RITUXIMAB OR CYCLOPHOSPHAMIDE FOR PRIMARY MEMBRANOUS NEPHROPATHY?

Van den Brand J and Ruggenenti P, *J Am Soc Nephrol*, 2017

203 patients with primary MN and persistent nephrotic syndrome

Treatments: - Rituximab *(One or four 375 mg/m²): n=100*
- Cyclophosphamide (1.5 mg/kg/day for 6-12 months) and Steroid: *n=103*
- Groups were comparable for gender, age, BMI, disease duration, blood pressure and eGFR

Site: - Bergamo (*Italy*) and Nijmegen *(The Netherlands)*

Serious events	Total number		Likely/possibly related		Unrelated	
	Rituximab	Cycloph.	Rituximab	Cycloph.	Rituximab	Cycloph.
Fatal	4*	9	0	5	4	4
- Sepsis from the respiratory tract	0	3	0	3	0	0
- Cancer*	1*	2	0	2	1	0
- Cardiovascular	3	2	0	0	3	2
- Death from unknown cause	0	2	0	0	0	2

*One case of lung cancer in a patient treated with steroids plus cyclophosphamide 61 months prior to rituximab

Table 1. Fatal serious adverse events in the two treatment groups. Five of the nine fatal events observed with steroid and cyclophosphamide were considered to be treatment-related whereas no fatal adverse event was related to rituximab.

Serious events	Total number		Likely/possibly related		Unrelated	
	Rituximab	Cycloph.	Rituximab	Cycloph.	Rituximab	Cycloph.
Non-fatal	**7**	**37°°°**	**0**	**33°°°**	**7**	**4**
Myelotoxicity	0	6°°	0	6°°	0	0
- Anemia	0	1	0	1	0	0
- Leukopenia	0	6°	0	6°	0	0
- Thrombocytopenia	0	1	0	1	0	0
Malignancy	2	6	0	6°	2	0
- Blood cancers	0	3	0	3	0	0
- Solid cancers	2	3	0	3	2	0
Major Cardiovascular Events	5	4	0	0	5	4
Thromboembolic events	0	7°	0	7°	0	0
- Pulmonary thromboembolism	0	3	0	3	0	0
- Deep venous thrombosis	0	4	0	4	0	0
Infections	0	8°°	0	8°°	0	0
Respiratory tract	0	3	0	3	0	0
Urinary tract	0	1	0	1	0	0
Sepsis from the Urinary tract	0	1	0	1	0	0
Cytomegalovirus	0	3	0	3	0	0
Other events	0	6°	0	6°	0	0
Osteonecrosis	0	1	0	1	0	0
Hemorrhagic cystitis	0	1	0	1	0	0
Diarrhea	0	2	0	2	0	0
Nausea	0	2	0	2	0	0

°p<0.05, °°p<0.01, °°°p<0.001, cyclophosphamide

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Table 2. Non-fatal serious adverse events in the two treatment groups. Serious adverse events, particularly those likely treatment-related, were remarkably more frequent in patients treated with steroid and cyclophosphamide than in those treated with rituximab

The impact of rituximab on patient quality of life

Patients receiving rituximab benefit from the improvement in symptoms associated with remission of proteinuria and discontinuation of other immunosuppressive medications. By contrast, in patients treated with steroids, alkylating agents, or calcineurin inhibitors quality of life is detrimentally affected by the toxicities of these medications, even when remission is achieved[92]. These considerations specifically apply to patients with PMN[98] and even to those with multiple relapsing forms of NS[99].

Optimal dosing of rituximab

The most frequently used rituximab treatment protocol involves a dose of 375 mg/m^2 once a week for 4 weeks, but eight-dose 'prolonged protocols', or 'extended protocols' with monthly infusions for two or three months following the standard four-dose regimen have also been used[100]. However, CD20 cells were found to be depleted from the circulation after a single dose of rituximab in patients with MN or systemic lupus erythematosus (SLE)[101,102].

A prospective 1:2 matched-cohort study compared the risk/benefit profile of a B cell-driven rituximab treatment with the standard four 375 mg/m^2 dose rituximab protocol in 36 patients with MN and NS refractory to conventional therapy[103]. Patients allocated to the B cell-driven protocol received a second infusion of rituximab only if they had >5 B cells

per mm^3 of peripheral blood after the first 375 mg/m^2 dose, which occurred in only one of the 12 patients in this group[103]. The two treatments promptly and persistently depleted circulating B cells in all patients and achieved a similar time-dependent reduction in proteinuria. However, adverse events and hospitalizations were less frequent with the B cell-driven approach, which was also fourfold less expensive[103] **(Figure 9. Left and Right Panels).** Thus, the B-cell driven protocol should facilitate access to rituximab even in resource-limited settings. Indeed, one 375 mg/m^2 dose of rituximab in an average 70 kg patient costs €3206,29 ($4,275)[104]. The alternative treatment with intravenous and oral steroids plus oral cyclophosphamide for 6 months at currently recommended doses costs approximately €450 ($600)[105]. However, this figure does not include the cost of frequent clinic visits to monitor blood cell counts and hospitalizations because of treatment-related adverse events. Considering that a 1-day hospitalization in a non-intensive care unit, including a Unit of Nephrology of Dialysis, costs €300–500 ($400–666)[106], just one admission would largely offset the costs saved with steroids plus alkylating agents versus rituximab therapy.

The current recommendation for patients with PMN is to use calcineurin inhibitors for at least 12 months before considering discontinuation[107]. In the USA, the average cost of a calcineurin inhibitor at doses used for MN is ~$700 per month[108]. To this expense must be added the cost of monitoring drug levels, and of blood pressure lowering medications needed to control treatment-induced hypertension. In the long-term, treatment costs will increase as >50% of these patients relapse within 12 or18 months after withdrawal of cyclosporine or tacrolimus, respectively[109,110]. These relapses will require further courses of calcineurin inhibitors and multiple relapses are associated with doubling of serum creatinine levels and development of ESKD[111,112]. Thus, additional costs will be needed for repeated courses of calcineurin inhibitors and to manage complications related to their chronic nephrotoxicity.

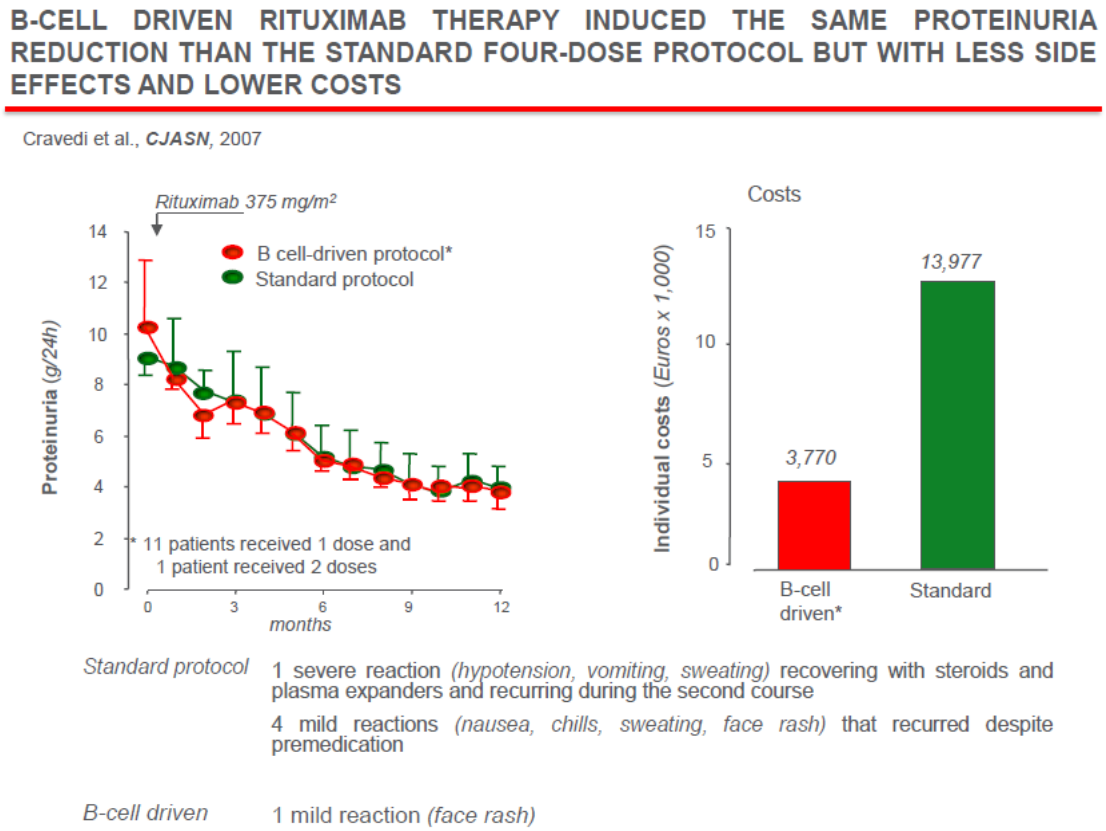

Figure 9. Cost-effectiveness of B-cell driven versus the standard four-dose Rituximab treatment protocols. The two protocols were similarly effective in reducing proteinuria (Left Panel), but the B-cell driven protocol was largely less expensive than the standard four-dose protocol and was also associated with a lower rate of adverse events.

Randomized controlled trials of rituximab versus supportive therapy or non-specific immunosuppression

GEMRITUX - In the prospective, randomized, controlled GEMRITUX clinical trial[113], two 375 mg/m^2 doses of rituximab were compared with non-immunosuppressive antiproteinuric therapy on the rate of complete or partial remissions in 75 patients with PMN and residual proteinuria >3.5 g/24-h despite maximal tolerated doses of ACE inhibitors or ARBs, statins, and diuretics. By 17 months after randomization the rate of complete or partial remission in rituximab group was almost twice that of controls (64.9% versus 34.2%, p=0.03). Consistently, seven patients treated with rituximab achieved complete remission as compared to only one control[113].

In the rituximab group, anti-PLA$_2$R autoantibodies were almost fully depleted from the circulation 3 months after randomization, whereas the antibody titer did not change appreciably in the control group throughout the observation period. Serum albumin concentration increased in rituximab-treated patients at 3 and 6 months compared with baseline but did not change in control patients. As previously observed with ACE inhibitors[114], serum albumin increase preceded proteinuria reduction by months[113]. A post-hoc analysis demonstrated that, at 6 months, more patients receiving rituximab than those in the supportive therapy group achieved a >50% reduction in proteinuria with at least a 30% increase in serum albumin levels (40.5% versus 13.2%; p <0.01)[113].

Notably, the rate and timing of complete or partial remission achieved by rituximab were similar to those previously reported with rituximab in uncontrolled series[115], and also to those reported in previous trials with steroid and alkylating agents at 6 months and 1 year of follow up[80,82]. Remarkably, the safety profile of rituximab therapy was similar to that of supportive therapy, a finding that supports safety data from previous uncontrolled studies[27,54–57,60,116].

MENTOR – In the MENTOR trial[93], 130 patients who had PMN, proteinuria of at least 5 g per 24 hours, and a quantified creatinine clearance of at least 40 ml per minute per 1.73 m^2 of body-surface area and had been receiving angiotensin-system blockade for at least 3 months were randomized to receive intravenous rituximab (two infusions, 1000 mg each, administered 14 days apart; repeated at 6 months in case of partial response) or oral cyclosporine (starting at a dose of 3.5 mg per kilogram of body weight per day for 12 months). The primary outcome was a composite of complete or partial remission of proteinuria at 24 months. At 12 months, 39 of 65 patients (60%) in the rituximab group and 34 of 65 (52%) in the cyclosporine group had a complete or partial remission (p=0.004 for non-inferiority). At 24 months, 39 patients (60%) in the rituximab group and 13 (20%) in the cyclosporine group had a complete or partial remission (p<0.001 for both non-inferiority and superiority) **(Figure 10).** Progressive loss of renal function was slower with rituximab than with cyclosporine over the whole trial period, probably owing to the chronic nephrotoxic effects associated with cyclosporine. Notably, among patients in remission who had PLA$_2$R-related disease, the decline in anti-PLA$_2$R titer was faster and of greater magnitude and duration in the rituximab group than in the cyclosporine group. As previously reported[21,27,37,60] the immunologic response to rituximab invariably preceded the clinical response. SAEs occurred in 11 patients (17%) in the rituximab group and in 20 (31%) in the cyclosporine group (p=0.06). Thus, rituximab was non-inferior to cyclosporine in inducing complete or partial remission of proteinuria at 12 months, was superior in maintaining proteinuria remission up to 24 months and was safer.

Based on the MENTOR data, rituximab should replace cyclosporine, the most frequently used immunosuppressive drug in the United States and Canada for the treatment of PMN[117]. Evidence that 35% of patients treated with rituximab achieved complete remission of the NS as compared to none of those treated with cyclosporine has major clinical implications because patients who have complete remission at some time during the course of the disease rarely progress to ESKD[4].

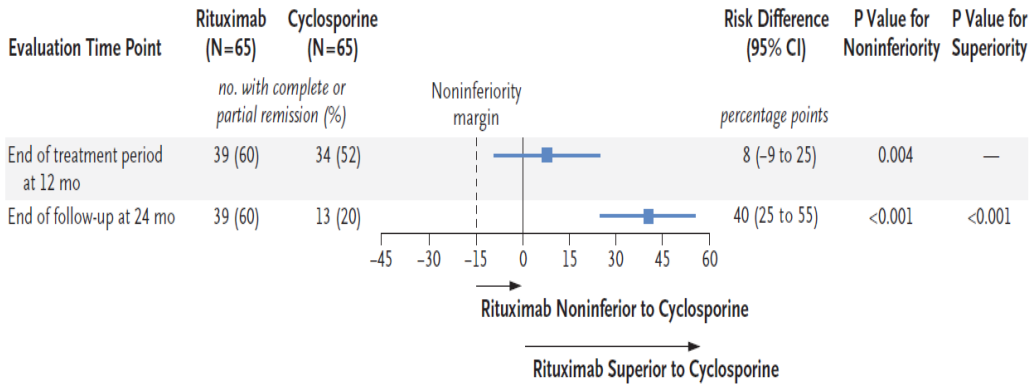

Figure 10. Composite Outcome of Complete or Partial Remission at 12 and 24 Months in the MENTOR Trial. Point estimates and two-sided 95% confidence intervals are shown for the treatment effect, defined as the risk difference for complete or partial remission between groups in the intention-to-treat analysis. The 0.004 P value for non-inferiority was significant. No test for superiority was performed for the secondary outcome of complete or partial remission at 12 months. At 24 months both the criterion for non-inferiority and the criterion for superiority of rituximab were met at a P value of less than 0.001. P values for non-inferiority are one-sided, and the P value for superiority is two-sided.

RI-CYCLO – In the RI-CYCLO pilot trial[118] 74 adults with PMN and proteinuria >3.5 g/d were randomly assigned to rituximab (1 g) on days 1 and 15, or a 6-month cyclic regimen with corticosteroids alternated with cyclophosphamide every other month. Despite the non-significant trend to a lower rate of complete or partial remissions with the cyclic regimen as compared to rituximab at 12 months, no difference in events could be detected any longer at 24 months after randomization. Moreover, changes in proteinuria and serum albumin levels up to 36 months of follow-up were virtually identical in the two treatment groups **(Figure 11).** Thus, as acknowledged by the Authors, considering the better long-term safety profile of rituximab, rituximab may be considered as a first-line therapy for PMN or for repeat treatments.

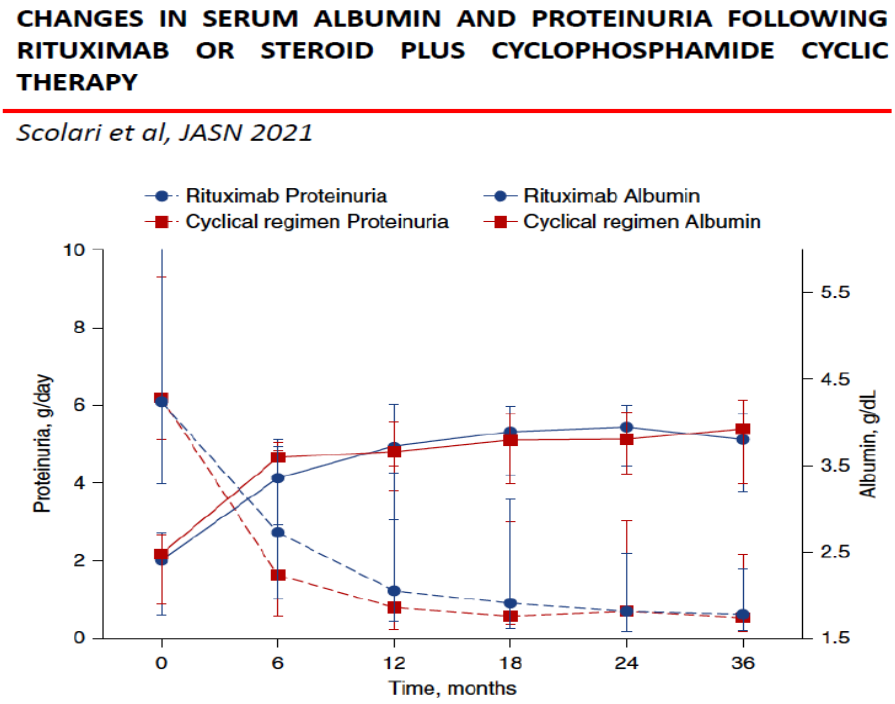

Figure 11. Proteinuria and serum albumin changes following randomization (month 0) in the RI-CYCLO trial. Changes in serum albumin levels mirrored those in proteinuria. Changes in the two parameters were virtually identical. Data are presented as median (IQR) over time, by assigned treatment.

STARMEN - The STARMEN randomized, open-label controlled trial of 86 patients with PMN and persistent NS after six-months observation assigned 43 each to receive six-month cyclical treatment with corticosteroid and cyclophosphamide or sequential treatment with tacrolimus (full-dose for six months and tapering for another three months) and rituximab (one gram at month six). Results showed almost 60% of remissions at 24 months and only 3 relapses after tacrolimus discontinuation[119], which supports the efficacy of rituximab even to prevent relapses of the NS in patients with PMN on calcineurin inhibitor therapy. This trial provides additional evidence that the high relapse rate upon treatment withdrawal, in addition to nephrotoxicity, is a major limitation that definitely undermines the role of calcineurin inhibitors in this context[93].

Rituximab and kidney transplant

PMN recurs in approximately 42% of kidney transplant recipients with proteinuria and decreasing graft function, and may result in increased risk of graft failure[120–124]. In these patients rituximab therapy can result in both clinical remission and histological resolution[122,125,126]. Approximately 80% of kidney transplant recipients have anti-PLA_2R antibodies, which seem to predict disease recurrence and response to anti-CD20 therapy[21,127,128]. Post-transplant per-protocol biopsies allow early diagnosis of recurrence before progression to severe disease[126]. Disease recurrence often occurs during the first year after transplant, although a second 'wave' of recurrences can be detected by per-protocol biopsies up to 5 years[126]. Initial recurrence may spontaneously recover in almost 30% of cases, as observed in native kidneys[8], possibly because of an immuno-modulatory effect of induction therapy that can result in anti-PLA_2R antibody titer reduction early after transplant[127]. Patients with proteinuria exceeding 1,000 mg per day have progressive disease[121,122] and may have an indication to rituximab therapy[126]. In one cohort study, treatment achieved persistent disease remission and histological resolution in 82% and 40% of patients, respectively, and invariably prevented kidney graft failure[126]. No patient required re-treatment: a remarkable change from previous experience[120–124]. Despite concomitant immunosuppression with corticosteroids, calcineurin inhibitors (or sirolimus in 3 cases), and mycophenolate mofetil, no serious infections were associated with rituximab, and only nonserious events were observed early after treatment[126]. The highest recurrence rate was observed in patients with severe proteinuria and, as previously reported[127,128], detectable circulating anti-PLA_2R antibodies at the time of transplant. However, recurrence can be observed also in one-third of patients without detectable anti-PLA_2R antibodies. Despite persisting PLA_2R antigen glomerular staining, in some patients anti-PLA_2R antibodies are not detected after transplant probably because transplant-related immunosuppression can inhibit autoantibody production[127].

Thus, PMN patients who are candidates for kidney transplantation should be advised that over 6 years they could have a recurrence in 50 to 60% of cases, with 30-35% of recurrences being observed during the first year post-transplant[126]. Although 60% of PMN recurrences are progressive, in most cases rituximab is effective particularly when applied early in the disease[126]. Close surveillance for proteinuria, albuminuria, and antibody titer is advised, particularly in patients at high risk of recurrence. Theoretically, rituximab prophylaxis could prevent post-transplant PMN recurrence and allograft injury[126], but should probably be administered several months before surgery because treatment effect is progressive over time[27].

Thus, early diagnosis and early B-cell targeting therapy could substantially reduce the risk of kidney graft loss because of PMN recurrence, a risk that in the era before rituximab accounted for 18–20% of allograft losses[129,130].

Failure of rituximab therapy

In the 25–30% of patients with PMN and NS who fail CD20-targeted therapy with rituximab, steroids plus cyclophosphamide and calcineurin inhibitors should be avoided owing to the associated adverse effects[3] and unknown efficacy as second-line therapy. In kidney transplant candidates conservative therapy is instrumental to avoid the risk of add-on, adverse interactions between immunosuppression and subsequent antirejection treatment.

Severe and irreversible chronic kidney lesions can account for approximately half of treatment failures, in the remaining cases intolerance or resistance to rituximab could have a role.

Intolerance to Rituximab – In patients who frequently relapse after initial remission, repeated exposures to rituximab may induce the production of antibodies against the murine portion of the drug (**Figure 4**, **Panel A**), that in addition to cause serious acute infusion reactions, can induce delayed immune-complex mediated hypersensitivity reactions including arthritis, arthralgias, myalgia and fever that are typical of serum-sickness and contraindicate additional rituximab infusions[3]. In this context human or

humanized monoclonal antibodies such as ofatumumab and obinutuzumab, respectively, could have an indication because they do not induce the production of anti-drug antibodies[131] and do not cross-react with pre-formed anti-rituximab antibodies that can also inhibit B-cell cytotoxicity with faster B-cell reconstitution, reduced remission rate and increased risk of early relapses[132]. Notably, in an adult patient with multi-relapsing PMN requiring repeated rituximab infusions, who eventually developed delayed serum-sickness and resistance to rituximab most likely explained by the development of inhibiting anti-drug antibodies (**Figure 12**), rescue treatment with the fully human anti-CD20 antibody ofatumumab was well tolerated, achieved antibody depletion and induced persistent remission of the NS for approximately two years (**Figure 13**). On relapse, retreatment with ofatumumab was uneventful and again effective in inducing disease remission.

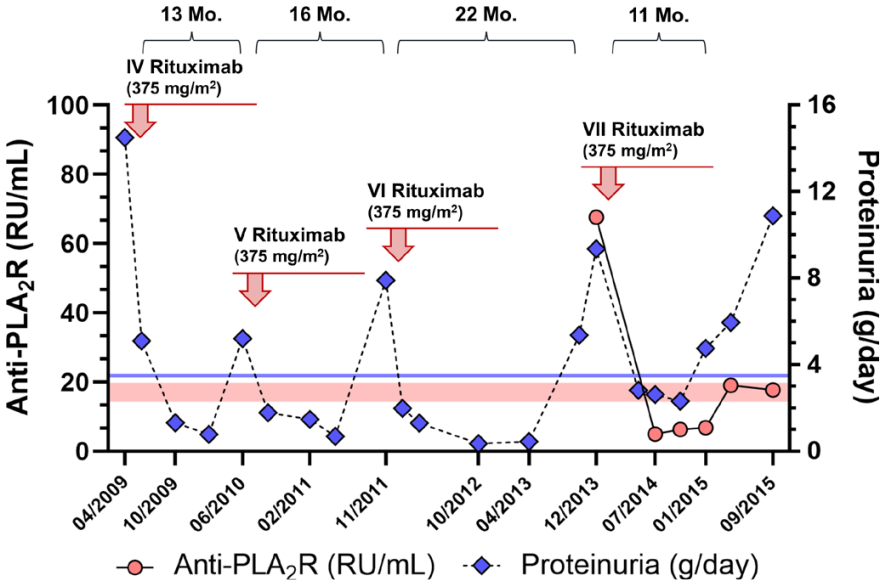

Figure 12. Time course of proteinuria and anti-PLA$_2$R antibody levels before and after the last four rituximab infusions. Red circles: anti-PLA$_2$R levels (RU/mL); blue diamonds: 24 hours proteinuria (g/day); red-colored area: borderline anti-PLA$_2$R range (14–20 RU/mL); blue line: proteinuria threshold for partial remission (<3.5 g/day). Time to relapse (months) from each infusion is shown above each panel. PLA2R, podocyte phospholipase A$_2$ receptor.

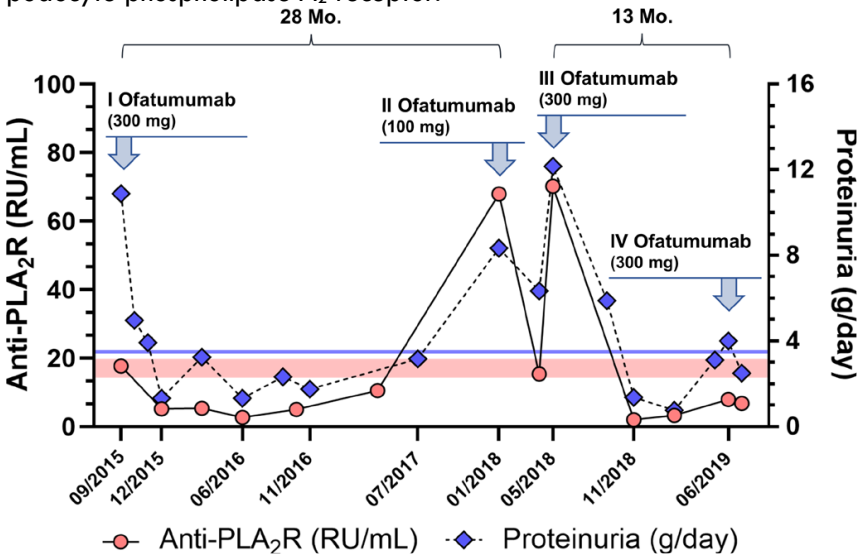

Figure 13. Time course of proteinuria and anti-PLA$_2$R antibody levels before and after treatment with ofatumumab. Red circles: anti-PLA$_2$R levels (RU/mL); blue diamonds: 24 hours proteinuria (g/day); red-colored area: borderline anti-PLA$_2$R range (14–20 RU/mL); blue line: proteinuria threshold for partial remission (<3.5 g/day). Time to relapse (months) from each infusion is shown above each panel. PLA$_2$R, podocyte phospholipase A2 receptor.

RESISTANCE TO RITUXIMAB - The B-cell surface antigen CD20 is a tetra-transmembrane protein involved in the phosphorylation cascade of intracellular proteins and B-cell activation, proliferation, and differentiation[133]. This protein protrudes from the surface of the B-cell membrane into the extracellular space by a small and a large loop that are binding sites for anti-CD20 monoclonal antibodies (**Figure 4, Panel B**)[59,134–136]. As observed in treatment-resistant B cell lymphomas, some B cells become resistant to rituximab-induced complement-dependent cytotoxicity because of changes or internalization of the large loop of the CD20 antigen, which prevents rituximab binding to its specific epitope. Second and third generation anti-CD20 monoclonal antibodies, such as obinutuzumab and ofatumumab, overcome this limitation by binding different epitopes on the CD20 antigen and are effective for the treatment of B-cell lymphomas[137] (with some exceptions[138]) and other blood malignancies[139] in patients who had previously failed rituximab therapy. Ofatumumab, specifically recognizes an epitope encompassing both the small and large extracellular loops of the CD20 molecule and one in the small extracellular loop (**Figure 4, Panel B**)[140], which seems to be closely related to effective C1q capture and complement mediated cytotoxicity[139]. The close binding proximity of ofatumumab to the cell membrane is likely to result in more efficient complement deposition on B-cell membranes, which might explain the cytotoxic effects of this agent on rituximab-resistant B cells. Ofatumumab has been approved by FDA and the European Medicines Agency (EMA) for the treatment of chronic lymphocytic leukaemia[141] and could have additional indications for some non-Hodgkin lymphomas and relapsing–remitting multiple sclerosis and rheumatoid arthritis[142]. It also achieved complete remission in five patients with focal segmental glomerulosclerosis or minimal change disease associated with rituximab-resistant NS[143].

Conceivably, changes in the CD20 antigen that prevent rituximab binding might be restricted to autoreactive B-cell clones that continue to produce nephritogenic antibodies despite depletion of the large majority of 'innocent' circulating B cells. Ofatumumab could be effective against this specific subset of autoreactive B cells. Thus, ofatumumab is a promising alternative to rituximab and is even less expensive[104].

Resistance to rituximab could also be explained by ineffective access of rituximab to lymphoid organs[144], which might result in incomplete or insufficient depletion of autoreactive B-cell clones[145], that may continue to differentiate into plasma cells with consequent continued production of nephritogenic antibodies[146], despite complete peripheral B-cell depletion. These processes might specifically involve B-cell clones in the spleen, bone marrow and inflamed tissues where memory B-cells with a specific phenotype and long-living autoreactive plasma cells are enriched[145,147]. Unlike rituximab, the type 2 anti-CD20 monoclonal antibody obinutuzumab. induces effective B-lymphocyte depletion not only in peripheral blood but also in lymph nodes[148] It is a safe and well tolerated fully humanized anti-CD20 monoclonal antibody that is not susceptible to internalization of the antibody complex[149], is more effective in inducing direct cell death[52,150] and potentiates the cytotoxic effect of natural killer cells with enhanced ADCC efficacy[151], even in PMN patients[152], including those who are rituximab-resistant and produce anti-rituximab antibodies[153–156]. The role of obinutuzumab in this context is under formal investigation (Clinical trial gov: NCT05050214).

B-cell inhibition can be achieved also by blockade of factors or cells that stimulate autoreactive B cells, such as type I interferon, T helper cells, or regulatory T cells, that might also prevent the development of short-lived plasmablasts and plasma cells[154]. A monoclonal antibody, belimumab, specifically targets the soluble form of B lymphocyte stimulator (BLyS), a tumor necrosis factor super family ligand that has a critical role in the differentiation and homeostasis of B lymphocytes. Via BLyS inhibition, belimumab might induce apoptosis and depletion of autoreactive B cells. In 14 patients with PLA_2R-related PMN and a urinary protein/creatinine ratio >400 mg/mmol[157]. belimumab significantly and progressively decreased anti-PLA_2R antibody titer by week 12, and reduced proteinuria together with normalization in serum albumin levels in those with overt NS, effects that seemed to parallel the changes observed after rituximab administration, but with an apparent delay of approximately 3 to 6 months (**Figure 14**). Conceivably, the faster effect of rituximab reflected immediate B-cell lysis, whereas the delayed effect of belimumab might reflect progressive 'exhaustion' of antibody-producing B cells secondary to BLyS binding and inhibition. Considering the different mechanisms of B-cell inhibition, rituximab and belimumab could be given in combination to synergistically inhibit autoreactive B-cell clones[158].

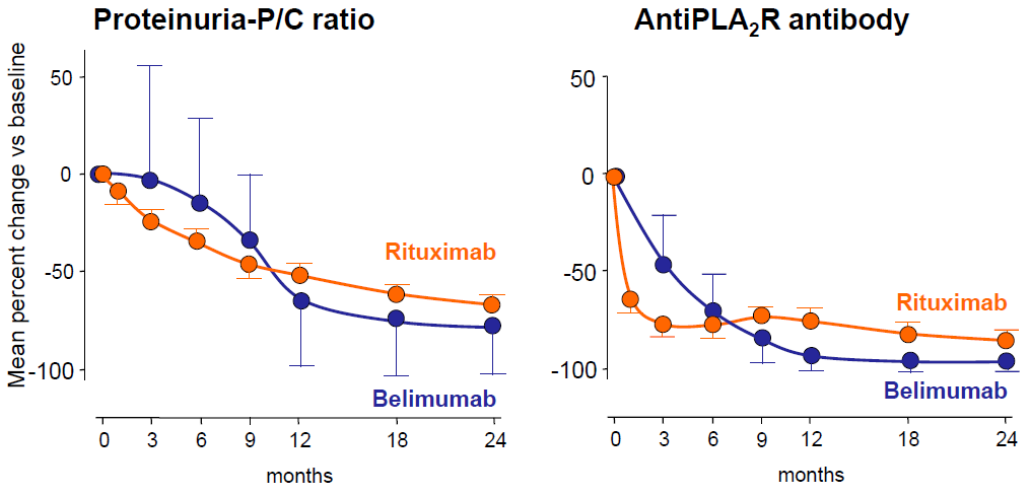

Figure 14. Comparison of outcomes following belimumab or rituximab therapy. Left Panel. Percentage change in urinary proteincreatinine ratio (or 24 h proteinuria) versus baseline[3]. **Right Panel.** Percentage change in anti-PLA_2R antibody titer versus baseline[3].

Targeting memory plasma cells

Autoantibodies against PLA_2R, THSD7A, or other unknown antigens, can be produced by two distinct antibody-producing-cell populations[159]: short-lived plasma cells and long-lived memory plasma cells. Short-lived plasma cells are usually generated in the spleen and lymph nodes from activated B cells. Upon exposure to antigens these cells proliferate and differentiate into plasmablasts (immature plasma cells), which invade the peripheral circulation, produce antibodies, and further differentiate into mature, short-lived, non-proliferating plasma cells. Activated B cell clones, however, can be disrupted by non-specific immunosuppressants, such as steroids and alkylating agents, as well as by anti B-cell antibodies, such as rituximab, ofatumumab and obinutuzumab, which have a direct cytolytic effect, or can be inhibited by other antibodies, such as belimumab, that may block growth factors and mediators of B-cell proliferation and differentiation. After disruption/inhibition of the autoreactive clones, the plasma cell pool is no longer fueled; short-lived plasma cells disappear within a few days of treatment and are no longer replenished.

By contrast, memory plasma cells are resistant to conventional immunosuppression and B-cell targeted intervention. These cells secrete antibodies independent of antigen contact or interactions with B cells and T cells and are involved in chronic humoral autoimmunity and treatment-refractory disease. The memory cell pool can also be enriched by plasmablasts, which invade survival niches in the bone marrow, lymph nodes, and inflamed tissue where they transform into long-lived memory plasma cells to sustain autoantibody production and chronic inflammation. Speculatively, upon re-exposure to antigens, memory cells could reactivate to plasmablasts and then convert to plasma cells and produce large numbers of antibodies[160].

Therefore, in patients with PMN, newly generated, short-lived plasmablasts attributable to B-cell hyperactivity are likely to produce most of autoantibodies at disease onset and at the time of relapses, whereas memory plasma cells produced as a result of earlier autoreactive B-cell activation can sustain autoantibody production despite therapy or disease relapses after initial remission. Conceivably, both pathways might differently contribute to autoantibody production in different patients and at different stages of the disease[161].

Memory plasma cells survive rituximab therapy because they do not express the CD20 antigen and continue to produce autoantibodies despite effective B-cell depletion from the circulation[147,161]. Plasma cells, however, strongly express CD38, a multifunctional cell surface protein that is expressed at low levels in other blood cells and solid tissues[162]. CD38-positive plasma cells have been observed to enrich chronically inflamed tissues and to secrete autoantibodies[147]. Therefore, autoreactive plasma cells could be a target for anti-CD38 monoclonal antibodies, such as daratumumab and felzartamab. Like anti-CD20 antibodies that were initially introduced for the treatment of B-cell lymphomas, these agents have been developed to kill malignant plasma cells[162] and could be tested in patients with plasma cell-mediated autoimmune diseases, including some forms of PMN.

Daratumumab is the first-in-class monoclonal antibody with a high affinity for CD38[163] that

induces cellular death via ADCC, antibody-dependent cellular phagocytosis (ADCP), and CDC[164,165]. Thus, also daratumumab could be a novel therapeutic option for patients with resistant PMN therapy[166,167]. However preliminary discouraging evidence in one patient with multi-resistant PLA_2R-associated PMN who eventually developed ESKD 24 months after daratumumab infusion, must be taken to indicate that the real role of daratumumab in the treatment of PMN needs to be tested in adequately powered clinical trials[168].

Felzartamab (MOR202) is a fully human recombinant monoclonal antibody against CD38 with in-vitro and in-vivo efficacy in experimental models of multiple myeloma. ADCC and ADCP are the principal mechanisms of action for felzartam-induced lysis of myeloma cells (https://ashpublications.org/blood/article/126/23/3015/135243/MOR202-a-Human-Anti-CD38-Monoclonal-Antibody. Accessed on January 2023). It is currently under investigation in phase I/IIa clinical trials in multiple myeloma[169]. In patients with relapsed or refractory multiple myeloma, felzartamab as monotherapy or in combination with standard therapy with dexamethasone, pomalidomide or lenalidomide was found to be safe and well tolerated[169]. In cohorts with concomitant treatment with dexamethasone, infusion-related reactions were reported in only 7% of the subjects, an event rate that is inferior to that observed during rituximab infusion after steroid pre-medication[92]. This remarkably good safety profile could be explained by the fact that felzartamab does not induce CDC, which is suspected to contribute to the infusion-related reactions observed with other monoclonal antibodies[170,171]. Moreover, no patient was reported to develop ADAs. Thus, CD38-targeted therapy with felzartamab might safely abrogate autoantibody-dependent mechanisms in patients with plasma-cell mediated forms of PMN who failed previous treatment with rituximab and second-generation anti-CD20 monoclonal antibodies such as ofatumumab. Thus, felzartamab therapy might have an indication for patients with PMN and NS resistant to standard immunosuppression or CD20 targeted therapy (Clinical Trial Gov Registration Numbers: NCT04893096 and NCT04145440). Notably, preliminary results of the open label, multi-national Phase Ib-IIa M-PLACE study in 30 patients with new-onset or relapsing/resistant PLA_2R-related PMN, show that nine 16 mg/kg felzartamab infusions over six 28-day cycles can achieve rapid and substantial reduction in anti PLA_2R titer. Whether this effect may safely translate into sustained remission of proteinuria is still under investigation (accessed on January 2003 at: https://www.asn-online.org/education/kidneyweek/2021/program-abstract.aspx?controlId=3601516). Notably, felzartamab does not appear to impair the immune response of PMN patients vaccinated with currently available replication-incompetent vector vaccines or mRNA vaccines against SARS-CoV-2[172]. Whether integrated disruption of autoreactive B-cell clones and long-living, memory plasma cells by combined anti CD20 and anti CD38 monoclonal antibody therapy may offer a novel perspective of therapy for more severe cases of PMN is worth investigating[166].

Other molecules, such as the proteasome inhibitor bortezomib, effectively deplete plasma cells, particularly activated plasma cells that, during forced production of circulating autoantibodies, are exposed to unfolded protein accumulation and consequent apoptosis[173]. A patient with PMN who had failed 6-month treatment with high-dose steroids achieved complete remission of the NS with bortezomib[174] that fully depleted circulating CD34 and CD138 positive cells and progressively reduced proteinuria over 1 year in another patient with rituximab-resistant, post-transplant recurrent PMN[160]. Bortezomib has been recently reported to achieve remission of the NS also in another patient with rituximab-resistant PMN[175].

Unfortunately, bortezomib has serious adverse effects, such as infections and neurotoxicity, which necessitate treatment interruption in most patients. These limitations should be overcome with the development of second-generation proteasome inhibitors that are as effective than bortezomib, but safer.

Complement inhibition

Complement is activated by antibody interaction with target antigens on the podocyte and at least part of the glomerular injury initiated by this interaction is complement-mediated **(Figure 3, Panel B).** Data in Heymann nephritis[176] and affected humans[177] converge to indicate that subepithelial immunocomplex deposits activate the classical pathway, the alternative pathway or the lectin pathway with recruitment of later-acting C5, C6, and C5b-9 and insertion of the C5b-9 membrane attack complex into podocytes with production of reactive oxygen species, damage of the glomerular basement membrane, and proteinuria. C5b-9 can also induces podocyte apoptosis with podocytopenia and impaired glomerular barrier sieving function, and proteinuria[2]. When C5b-9 deposition is associated with C4d and C3 deposits, the disease is more

severe and has a worse outcome with more treatment failures and decreased kidney survival[178]. Complement activation appears to be involved also in the pathogenesis of tubulointerstitial injury with tubulointerstitial atrophy and fibrosis typical of PMN[179,180]. Thus, complement-targeted treatments may be effective in PMN, by limiting glomerular injury until the effect of autoantibody inhibition progressively emerges and by directly protecting against tubulointerstitial damage[177].

Eculizumab is a recombinant, humanized monoclonal antibody that could be a logical option for PMN therapy because it directly inhibits the function of the terminal complement pathway through C5 binding and blockade of the cleavage of C5 into C5a and C5b[181], thereby preventing the production of the anaphylatoxin C5a and the assembly of C5b-9[182]. However, one, unfortunately unpublished, prospective, randomized, clinical trial did not demonstrate any antiproteinuric effect of four-month eculizumab therapy (8 mg/kg every 2 or every 4 weeks) as compared to placebo in 117 patients with PMN. Data were most likely inconclusive because under-dosing of eculizumab resulted in ineffective complement inhibition[174]. Alternatively, treatment failure could be explained by the pathogenic role of complement effectors in addition to C5b-9, that are not affected by C5 blockade, such as the soluble complement activation fraction C3a[183]. Finding that in glomeruli of patients with PMN there was an over-expression of C3aR that positively correlated with proteinuria and that in Heymann nephritis rats C3aR blockade attenuated proteinuria, electron-dense deposition, foot process width and glomerular basement membrane thickening confirms that C3a anaphylatoxin is a crucial effector of complement-mediated podocyte damage in PMN and that, unlike C5 blockade, the C3aR antagonist could be a potentially viable treatment for the disease[183].

Thus, novel complement inhibitors including oral agents, recombinant proteins, small molecules, new monoclonal antibodies, small interfering RNA agents, and approaches that upregulate natural complement inhibitors will become available for clinical use in the next few years[184–186]. Finding that the inhibitor of the alternative complement pathway LNP023 effectively reduced proteinuria in Heymann nephritis[187] might provide a robust rationale for clinical studies testing complement inhibitor add-on therapy to promptly stop proteinuria while awaiting the clinical effect of rituximab.

Depleting Autoreactive B-Cells and Inducing Immunotolerance

Chimeric antigen receptor (CAR) T cells are genetically engineered to express an artificial T cell receptor directed against an antigen of interest: they are currently used in cancer immunotherapy[188] and have been reported to deplete $CD19^+$ B-cells and inhibit autoantibody production in a murine model of lupus[189]. Chimeric autoantibody receptor T cells (CAAR T cells) are a variant of CAR T cells that contain specific antigen domains and destroy autoreactive B cells upon binding to B-cell specific autoantibodies. In an *in vivo* model of pemphigus vulgaris, an autoimmune disease of the skin mediated by IgG autoantibodies against desmoglein 3 (Dsg3), T cells were specifically engineered to specifically recognize B cells that secrete anti-Dsg3 antibodies and to contribute to their precise and efficient disposal[190]. This pioneering approach might also be relevant to exerting antigen-specific immunosuppression in other B-cell mediated autoimmune diseases whose autoantigens have been identified, such as PMN. The generation of CAR Tregs is also a promising option to suppress autoimmune manifestations in diseases such as PMN characterized by a deficiency of regulatory T cells resulting in a loss of self-tolerance[191]. Nanoparticles with autoimmune disease-relevant peptides bound to major histocompatibility complex class II molecules could also be used to induce antigen-specific Tregs that promote the differentiation of B-cells into disease-suppressing regulatory B-cells[192]. Whether these new biotechnologies may have a role in the treatment of refractory PMN is therefore worth investigating[193].

Other potential therapeutic options

Upon binding to antigens such as CD38, CD138, and CD52, which are expressed on plasma cells, including autoreactive memory plasma cells[194], polyclonal antithymocyte globulins (ATGs) could achieve complete and sustained remission in patients with severe autoimmune diseases refractory to conventional immunosuppression. The process would involve an 'immunoablation' followed by the reconstitution of an 'adapted' immune system devoid of autoreactive long-lived memory plasma cells and which is, therefore, self-tolerant[195]. This immunoablation might explain why treatment-resistant PMN rarely reoccur in kidney transplant recipients, and why anti-CD20 targeted therapy is more effective in kidney grafts than in native kidneys. Unfortunately, the potentially devastating effects of even a transient ablation of the immune system do not justify this therapeutic

approach to PMN. Specific adhesion molecules inhibitors might prevent plasma cell homing and survival in the bone marrow niche and recruitment of inflammatory cells into the bone marrow or inflamed tissue. Ideally, novel drugs should specifically disrupt autoreactive plasma cells involved in the production of anti-PLA_2R or anti-THSD7A autoantibodies without affecting plasma cells that secrete protective antibodies[159]. Peptides that interact with autoreactive B cell antigens[184] and non-peptide antagonists binding specific nephritogenic epitopes of the antigen could also be implemented (**Figure 3, Panel C**)[2].

Conclusions

After the first report of rituximab efficacy in PMN[54], major advances in the understanding of disease mechanisms have led to a novel perspective on treatment. The integrated evaluation of serum autoantibody titer and proteinuria, together with serum albumin levels in patients with overt NS could guide diagnosis of PMN and individually tailored treatment protocols. Conventional, nonspecific, and toxic immunosuppressive regimens will become treatments of the past[7], to be replaced by more disease-specific and safer medications, such as B-cell targeting monoclonal antibodies and autoreactive plasma cell inhibitors, paving the way for a novel therapeutic paradigm based on the principles of precision medicine and personalized therapy[196]. Consistently, in the KDIGO 2021 clinical practice guideline rituximab is recommended as a first-line regimen for patients with PMN and moderate to high-risk of progression to kidney failure[197]. Complex predictive models to identify which patients to treat and when[198] will no longer be needed, and even the most frail patients with severe disease, who were previously left untreated to avoid the toxicity of non-specific immunosuppression, might benefit from new, safer therapeutic options. Treatment could be anticipated at earlier and milder stages of PMN to more effectively prevent chronic and potentially irreversible histological changes.

AUTHORS CONTRIBUTION

PR researched data for the article and wrote the initial draft and the final manuscript. GR contributed to discussion of the article's content and reviewed and edited the manuscript before submission. Both Authors approved the final version of the manuscript and take the responsibility of its submission

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CONFLICTS OF INTEREST

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