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Rituximab no tratamento de doenças glomerulares
The role of rituximab in the treatment of glomerulopathies

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RITUXIMAB NO TRATAMENTO DE DOENÇAS GLOMERULARES

THE ROLE OF RITUXIMAB IN THE TREATMENT OF GLOMERULOPATHIES

A systematic review

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Abstract

Background: In the past decades, biological therapies have revolutionized the treatment of the vast majority of immunological diseases. Rituximab (RTX), a chimeric anti-CD20 monoclonal antibody, was first used in the treatment of B-cell malignancies, but soon extended to other immunological diseases such as rheumatoid arthritis, pemphigus vulgaris and kidney disorders. The abrupt increase in the number of published articles on this drug has shed some light to its potential efficacy and safety in the field of glomerular disease.

Objectives: We aim to describe RTX's pharmacokinetics and pharmacodynamics and summarize the latest evidence on RTX's efficacy and safety in the treatment of glomerulopathies including membranous nephropathy (MN), anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV), lupus nephritis (LN), minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), immunoglobulin A nephropathy (IgAN), hepatitis C virus (HCV) associated cryoglobulinemic glomerulonephritis (GN) and other GN.

Methods: We conducted a systematic review of the most important data available on the use of RTX in glomerular diseases. We included published randomized clinical trials (RCT), meta-analysis and international guidelines, as well as registered on-going clinical trials.

Conclusion: Several RCTs have been conducted to study RTX use, being MN and AAV the clinical entities where the impact of this evidence was most notorious. The Kidney Disease: Improving Global Outcomes (KDIGO) 2020 guidelines on GN now recommend RTX as a first line therapy in MN patients with moderate to high risk of progressive loss of kidney function. Likewise, RTX in combination with glucocorticoids (GC) stands as a possible first line initial treatment in patients with AAV. It is also a suitable first line option for maintenance therapy. Additionally, RTX may be used as an alternative or in addition to initial therapies in class III, IV or V in patients presenting active non-responding/refractory LN, although there is no robust evidence to support this recommendation. Finally, the KDIGO 2018 guidelines on the treatment of HCV related kidney disease recommend RTX as the first line therapy in patients with histologically active HCV associated glomerular disease who do not respond to antiviral therapy, particularly those with cryoglobulinemic kidney disease. As for the other GN, we still lack sufficient clinical trials in order to establish the possible role of RTX. Currently, there are several ongoing studies which will bring valuable information to further establish RTX's role in the treatment of GN.

Keywords

Anti-CD20; immunosuppression; glomerulopathies; rituximab; therapeutic indications.

Introduction

RTX is a chimeric IgG1 murine/human monoclonal antibody with binding specificity to CD20 antigen, thereby acting by depleting B-cells. Given the role of B-cells in the pathogenesis of many immunological mediated kidney diseases, attention has been focused on this drug and major changes are rising on the standard of care of several kidney diseases.

RTX is growing stronger as a first-line therapy not only in glomerular diseases but also in kidney transplantation, and several RCTs and meta-analysis have showed sustained clinical improvement when compared to previous standard therapies.

Considering the vast literature and information about RTX in nephrology, we propose to systematically review the most recent studies with greatest impact in the treatment of glomerular pathologies.

Methods

The following databases were searched between September 2020 and March 2021: PubMed, EMBASE, the Cochrane Library and the website clinicaltrials.org. We used free text and the MeSH terms “rituximab”, “CD20 antibody”, “rituximab CD20 antibody”, “Mabthera”, “glomerular disease”, “glomerulopathy”, “glomerulonephritis”, “membranous nephropathy”, “ANCA vasculitis”, “vasculitis”, “pauci-imune”, “systemic lupus erythematous”, “lupus nephritis”, “minimal change disease”, “FSGS”, “Focal segmental glomerulosclerosis”, “Cryoglobulinemia”, “HCV glomerulonephritis”, “IgA nephropathy”, “IgA vasculitis”, “nephrotic syndrome”, “nephritic syndrome”. For the included articles, we used the tools “reference lists” and “related articles” of PubMed to increase our search. There was no restriction on publication date but we only selected articles in English and Portuguese. When multiple reports describing the same sample were published, the most recent or most complete report was used.

Results

1. Historical context

In August 1990, IDEC Pharmaceuticals started to develop RTX by immunizing mice with a human B-cell line. By January 1991, a murine antibody (2B8) capable of recognising CD20 was identified and led to the creation of an engineered chimeric antibody (C2B8) by fusing the light and heavy chain variable domains of 2B8 and the human k-light chain and Y1 heavy chain constant regions. RTX was first produced by the ovary cell of a Chinese hamster during the spring of 1992.(1,2) Five years later, in 1997, the Food and Drug Administration (FDA) approved RTX's use for B-cell lymphomas. For almost a decade, it was the top-selling oncology drug and has improved the outcomes in all B-cell malignancies.(3) As our understanding of the mechanism of action of RTX became better, it's use has been extended to a broader range of immune-mediated diseases, such as rheumatoid arthritis, thrombotic thrombocytopenic purpura and renal disorders.(2,4,5)

2. Mechanism of action

Evidence for multiple mechanisms of RTX action has been reported. The most established is B-cell depletion, and it has shown that one course of RTX effectively depletes B-cells for a 6 to 9 months period in 80% of the patients. B-cell depletion occurs by apoptosis, complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity.(6)

CD20 acts as a calcium channel and is associated with a number of protein kinases. When RTX binds to CD20 a cascade of intracellular signals initiates: caspase-3 activation leads to B-cell apoptosis; complement activation by the Fc portion of the antibody which leads to cell lysis; antibody mediated cytotoxicity by natural killer cells, macrophages and other effector cells.(2)

In addition to B-cell depletion, there's growing evidence suggesting a direct effect of RTX in podocyte function. RTX binds to sphingomyelin phosphodiesterase acid-like 3b (SMPDL-3b) protein and regulates acid sphingomyelinase (ASMase) activity, preventing their downregulation and directly affecting podocyte function.(7,8)

By binding to the 50 kD SMPDL-3b isoform, which is found in podocytes' lipid raft, RTX stabilizes this protein and prevents the actin cytoskeleton disruption of podocytes in glomerular diseases.(7,9) ASMase is a lipid hydrolase that cleaves sphingomyelin into ceramide, a pro-

apoptotic lipid.(10) Evidence suggests that RTX preserves ASMase activity in patients with recurrent FSGS.(11)

3. Safety

CD20 is expressed on most B cells, with the exception of stem cells, pro B cells and normal plasma cells. In addition, there is no evidence suggesting that CD20 is found free in circulation or expressed on other normal cells of the body. This fact makes RTX an enticing immunosuppressive agent in terms of safety and effectiveness.(2,3)

On another hand, being a chimeric monoclonal antibody, RTX retains the murine CD20-binding Fab regions, but uses a human Fc portion. This structure allows RTX to be less immunogenic, inducing less human anti-mouse antibody response.(12) Therefore, RTX has been widely used and is considered a safe drug with the majority of adverse events being minor infusion reactions. However, the nephrologist should be aware of the most frequent and severe possible side effects of RTX as well as how to react if such situations happen.

3.1. Infusion-related reactions

Cytokine-mediated infusion related reactions (IRR) are the main adverse events observed while administering RTX.(4,13). IRR may range from mild to severe and are experienced most frequently during the first infusion of RTX.(4)

Common mild to moderate symptoms include fever, chills, rigors and myalgia. Severe symptoms, characteristic of cytokine release syndrome, may include hypotension and bronchospasm and are experienced by approximately 10% of RTX users but anaphylaxis is rare. Fatal IRR are very rare, occurring in <0,1% of patients.(4,14)

Premedication protocols have been empirically derived from centers with experience in monoclonal antibody administration, rather than established through randomized trials. Therefore, despite the use of premedication patients must be monitored closely during and immediately following all infusions. A standard premedication regimen is paracetamol 1000 mg, chlorpheniramine 10 mg IV or oral diphenhydramine 50 mg and methylprednisolone 100 mg, given at least 30 minutes before the first and second infusion of RTX. The benefit of GC was addressed in the placebo-controlled Dose-Ranging Assessment International Clinical Evaluation of RTX in Reumathoid Arthritis (DANCER) trial, which showed that a single dose

of methylprednisolone (100 mg) given 30 minutes before beginning the RTX infusion reduced the frequency and intensity of first IRR while oral GC conferred no additional benefit.(15)

Additionally, RTX administration should initiate at 50 mg/h and increase every 30 minutes until a 400 mg/h rate is reached. It is possible to initiate RTX at higher doses if patients have a good tolerance profile.(4,13)

3.2. Hepatitis B virus reactivation

Evidence has shown that the depletion of B-cells achieved by the use of RTX affects the production of neutralizing antibodies, creating a vulnerable environment where hepatitis B virus (HBV) can proliferate. Considering that approximately 1 out of 3 people has been exposed to HBV infection worldwide, many of our patients subject to immunosuppressants can be at risk.

The onset of HBV reactivation may occur anytime from the first 2 weeks of therapy to a year after discontinuation of immunosuppressants. Patients with positive HbsAg as well as HbsAg-negative patients with positive anti-HBc are considered at high risk for reactivation (at least 10% incidence rate).(16,17) Screening for HBV prior to initiating RTX is recommended and it is consensual that HBsAg, anti-HBc and anti-HBs should be tested before initiating treatment with RTX.(4,18,19)

According to current guidelines, all HbsAgs, anti-HBc and anti-HBs negative patients should be vaccinated against HBV(19) and most authorities advocate for prophylactic treatment for HbsAg positive patients. There is no consensus regarding treating HbsAg-negative/anti-HBc positive patients(4,19), but HBV-DNA and alanine aminotransferase testing every 3 months is advocated by the American Society of Clinical Oncology in patients with resolved hepatitis B history. If HBV-DNA is detected, antiviral treatment should be provided.(19)

Antiviral prophylaxis may be initiated 2 to 4 weeks prior to treatment with RTX in patients with inactive HBV and should be maintained until 12 months after the last dose of this drug because of delayed immune recovery.(19) Nevertheless, there have been reported cases of HBV reactivation more than two years after RTX cessation.(4)

3.3. Hypogammaglobulinemia

Hypogammaglobulinemia has been described in literature as an adverse effect of RTX therapy, however the exact incidence is unknown. Different trials have showed variable frequencies of hypogammaglobulinemia, varying between 11.8% and 56%(20) and that it seems to be influenced by the patients primary disease. In AAV, it can reach >50% of patients while in rheumatoid arthritis, RTX-induced hypogammaglobulinemia is rare.(21)

Risk factors for the development of hypogammaglobulinemia include GC therapy, prior cyclophosphamide (CYP) exposure and low baseline Ig level.(4,21) A large cohort study of 8633 participants, reported that 85.4% of patients did not have immunoglobulin levels dosed before initiation of RTX. In addition, there was evidence that patients with hypogammaglobulinemia prior to RTX treatment developed a more severe hypogammaglobulinemia. The authors suggest that Ig level screening before RTX should be considered in order to identify patients at a high risk of severe hypogammaglobulinemia.(22)

Nonetheless, the clinical significance of hypogammaglobulinemia is still controversial and while some studies suggest an association between hypogammaglobulinemia and an increased risk of infection(21–24), others do not report an increased risk.(25,26)

For patients that develop severe infections related to RTX induced hypogammaglobulinemia, IV immunoglobulin has been used, but there are no formal recommendations.(4)

3.4. Pregnancy and breastfeeding

Pregnancy constitutes a contraindication for RTX therapy since it crosses the placenta after 20 weeks of gestation.(27) Effective contraception counselling should be given to both sexes in order to avoid pregnancies during treatment and the following 12 months. Regarding breastfeeding, we lack sufficient evidence to guarantee that it is safe.(28) While the European Alliance of Associations for Rheumatology (EULAR) advocates against RTX therapy during breastfeeding, the European Medicines Agency (EMA) and the FDA agree that the unknown risks should be weighed against the known benefits.(4)

3.5. Contraindications

According to EMA, RTX should not be administered in patients with any of the following: hypersensitivity to the drug and/or other murine proteins; active severe infection (acute or

chronic); severely weakened immune system; severe heart failure (New York Heart Association class IV); pregnancy.(29)

4. Therapeutic uses in glomerular disease

4.1. Membranous nephropathy

MN is characterized by the deposition of immune complexes in the subepithelial layer of the glomerular basement membrane with little or no cellular proliferation and infiltration.(30) Primary MN occurs in 75-80% of patients, compared to 20-25% in secondary MN (secondary to malignancies, systemic lupus erythematosus (SLE), non-steroidal anti-inflamatory drugs or infections).(31)

Regarding primary MN pathogenesis, the discovery of the podocyte M-type phospholipase A2 receptor 1 (PLA2R1) in 2009, as the target antigen in 70% of MN cases, was a large step forward in our understanding of this disease. Anti-PLA2R1 antibodies, both in serum as in histopathology, are nowadays important non-invasive diagnostic and prognostic markers.(31,32) Thrombospondin type 1 domain-containing 7A (THSD7A) is the binding antigen in approximately 3-5% of cases of primary MN, and was first described in 2014. In addition, approximately 15 to 20 percent of cases of suspected primary MN are both serologically and tissue negative for PLA2R and THSD7A, which indicates that there are as-yet undiscovered antigens in primary MN.(33) The 2020 KDIGO clinical practice guidelines on glomerular disease propose that anti-PLA2R1 and anti-THSD7A provide an accurate biomarker for MN, with high sensitivity and specificity, suggesting that for selected patients, kidney biopsy may no longer be necessary.(34)

MN is the primary glomerulopathy in which RTX was the most revolutionary. Several RCTs have been published comparing RTX with other more established therapies, with non-inferior results towards RTX. Nowadays, RTX is the first-line immunosuppressive therapy for moderate- and high-risk patients who have normal or near-normal kidney function.(34)

Therapy for MN is dependent of patients' risk of progressive disease, and immunosuppressive drugs are restricted to patients considered at risk for progressive kidney injury. Figure 1, adapted from KDIGO clinical practice guidelines on glomerular diseases, summarizes the risk profile of MN and indications for specific treatments.(34)

When comparing the therapeutic scheme of KDIGO 2020 with the previous 2012 guidelines, it is notorious that RTX represents a major change in therapeutics approach for this

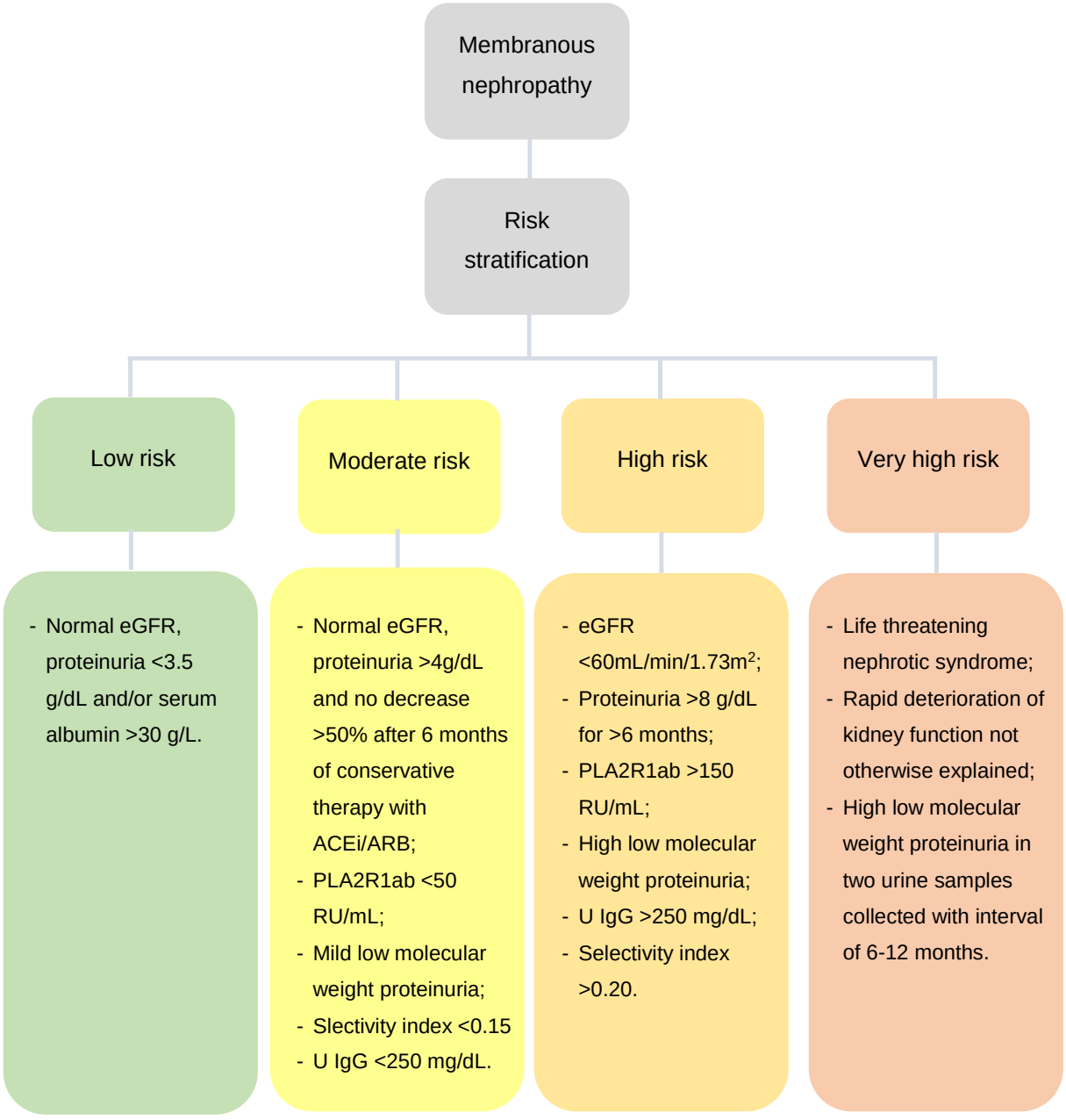

Figure 1 – Risk assessment criteria of progressive loss of kidney function in MN (adapted from 2020 KDIGO clinical practice guidelines on glomerular disease.(34)

ACEi: angiotension-converting enzyme inhibitor; ARB: angiotensin receptor blocker; eGFR: estimated glomerular filtration rate; IgG: immunoglobulin G; PLA2R1ab: antibodies against podocyte M-type phospholipase A2 receptor 1.

glomerular disease: in 2012, there is no reference to RTX while in 2020 it represents the first-line therapy for moderate and high risk patients.(34,35) These updated recommendations come after the publication of multiple clinical trials that we summarized in table 1.

The first multicentric RCT comparing non-immunosuppressive anti-proteinuric treatment (NIAPT) alone with NIAPT plus RTX in patients with primary MN and persistent nephrotic syndrome (NS) (moderate risk) was GEMRITUX, published in 2017. It included 75 patients with persistent proteinuria greater than 3.5 g/day after six months of supportive treatment. At six months there was no significant difference in complete or partial remission of proteinuria, estimated glomerular filtration rate (GFR) or serum creatinine between groups, however, serum albumin levels were higher in those treated with RTX (3.0 versus 2.4 g/dL) and PLA2R1 antibodies disappeared in a greater proportion in patients receiving RTX (50% versus 12% percent, $p<0.004$). During the observational phase of the study, 24 months after treatment, the NIAPT plus RTX group achieved 64,9% proteinuria remission vs 34,2% in the NIAPT group ($p<0.01$).(36)

This trial revealed that RTX is effective in achieving immunological and proteinuria remission and showed that the decline of anti-PLA2R1 antibodies occurs several months before the decrease of proteinuria, which is an indicator that immunological remission can be used as an early marker of remission.(36)

The MN trial of RTX (MENTOR), published in the New England Journal of Medicine in 2019, was a multicentre trial that randomized 130 patients with proteinuria ≥5 g/day and a GFR ≥40 mL/min/1.73m^2 (moderate risk patients), with at least three months of supportive care only. It aimed to compare RTX and cyclosporine effect on inducing and maintaining complete or partial remission of MN based on proteinuria reduction – primary endpoint was a composite of complete (proteinuria <0.3 g/day with serum albumin ≥3.5 g/dL) or partial (reduction of proteinuria >50% and between 0.3-3,5 g/day) proteinuria reduction at 24 months. Partial or complete remission was achieved by 60% of patients in the RTX branch and by 52% of patients in the cyclosporine group at 12 months ($p=0.004$), suggesting that RTX was non-inferior to cyclosporine in a 12-month timeframe. Despite that, at 24 months, the RTX group achieved a significantly higher rate of remission (60% vs 20%, $p<0.001$). Complete remission was also superior in the RTX group with 35% vs 0% in the cyclosporine branch. Also, and as a secondary endpoint, among patients who achieved complete or partial remission at 24 months, GFR was higher in RTX group when compared with cyclosporine, 96 versus 72 mL/min/1.73/m^2 at 12 months and 100 versus 87 mL/min/1.73/m^2 at 24 months, respectively. Serious adverse events occurred in 17% of patients in the RTX group compared with 31% in the cyclosporine.(37) This important RCT showed that RTX was more effective than cyclosporine for moderate risk patients with a better safety profile, and revolutionized the treatment of MN.

The largest trials with RTX in MN compare RTX with calcineurin inhibitors in moderate risk patients, and favour in a sustained way the therapy with RTX especially because of lower relapse rates at a longer term. However, there are few trials comparing RTX to cytotoxic therapies including CYP, especially in high-risk groups.

The sequential therapy with tacrolimus and RTX in primary MN (STARMEN) trial, published in 2020, compared RTX-tacrolimus sequential therapy with cyclic alternating treatment of GC-CYP in the induction and maintenance of NS remission in a population of 86 patients with persistent NS. The composite primary endpoint of partial/complete proteinuria remission was observed in 83.7% of patients in the GC-CYP branch at 24 months, with 60% of the patients achieving complete remission. The group subject to RTX-tacrolimus treatment had a 58.1% partial/complete proteinuria remission rate at 24 months, with only 26% achieving complete remission. The GC-CYP regimen was also superior at decreasing proteinuria over the course of 24 months from a median 7.4 g/day at baseline to 0.35 g/24h. In the RTX-tacrolimus group, it reduced from a median 7.4 g/day at baseline to 1 g/day. Additionally, immunological response was better in the CYP group with 77% and 92% of patients achieving remission at 3 and 6 months, respectively, compared to 45% and 70% in the RTX-tacrolimus group. The Ponticelli regimen was not only more effective but it was also faster in inducing remissions (53% vs 27,9% at 3 months).(33) This evidence favours cytotoxic therapy with CYP, especially for patients with high or very high-risk of disease progression.

In March 2021, the RTX or CYP in the treatment of MN (RI-CYCLO) randomized trial was published in the Journal of the American Society of Nephrology. The investigators randomized 74 patients with MN and proteinuria >3.5 g/day to RTX or 6-month cyclic regimen with GC alternated with CYP every other month. The primary endpoint of partial/complete proteinuria remission was achieved in 62% patients in RTX versus 73% in CYP at 12 months, which was statistically non-significant. At 24 months, the probability of partial/complete proteinuria remission was 83% for RTX versus 82% for CYP, with a similar rate of adverse effects (19% vs 14%). This pilot trial found no signal of more benefit or less harm associated with RTX versus a cyclic GC-CYP regimen in the treatment of MN, but a larger sample size is needed to give more power to this comparison.(38)

On another note, relapsing of MN is defined by some authors as a >3.5 g/24h increase in proteinuria in patients who achieved remission, but the KDIGO 2020 guidelines suggest that, in order to distinguish relapse from resistant disease, proteinuria-creatinine ratio and serum albumin should also be evaluated. An increase in proteinuria accompanied by serum albumin levels decrease in a patient with partial remission signals relapse. In the event of a protein-

Table 1 - Overview of clinical trials of rituximab in membranous nephropathy					
Reference	Patients (n)	Main inclusion criteria	Treatment schemes	Main endpoints/outcomes	Results
Segarra et al. 2009 Published in JASN (83)	13	MN GFR >60mL/min >=4 CNI-responsive relapses of nephrotic proteinuria	Weekly 375 mg/m2 RTX infusions for 4 weeks	% of patients withdrawing CNIs without relapsing % of patients with CR or PR 30 months after CNI withdrawal	100% of patients withdrawn CNIs without relapse 100% of patients were in remission 30 months after CNI withdrawal Proteinuria decreased significantly (p=0.0003) GFR increased significantly (p=0.0002)
Fervenza et al. 2010 Published in JASN (84)	20	Biopsy proven MN Persistent proteinuria >5 g/24h CC >=30 ml/min/1.73 m2	Weekly 375 mg/m2 RTX infusions for 4 weeks	Change in proteinuria at 12 and 24 months Nº of patients at PR or CR at 24 months Changes in GFR	Proteinuria decreased from baseline 11.9 ± 4.9 g/24h to 4.2 ± 3.8 g/24h at 12 months and 1.7 g/24h at 24 months (p<0.001) 4 patients achieved CR
Busch et al. 2013 Published in CN (85)	14	Biopsy proven MN 1-4 relapses	Monthly 375 mg/m2 RTX infusions for 4 months	Change in proteinuria Change in CC Nº of patients at PR or CR	Proteinuria decreased from baseline 5.5 g/24h to 1.8 g/24h at 3 mo (p=0.012) CC remained stable for the same time period

CC: Creatinine clearance; CN: Clinical nephrology; CNI: Calcineurin inhibitor; CR: Complete remission; CYP: Cyclophosphamide; GC: Glucocorticoids; GFR: Glomerular filtration rate; JASN: Journal of American Society of Nephrology; KI: Kidney International; MN: Membranous nephropathy; NE: Nephron Extra; NEJM: New England Journal of Medicine; NIAPT: Non-immunosuppressive anti-proteinuric treatment; NS: Nephrotic syndrome; PLA2R1: Podocyte M-type phospholipase A2 receptor 1; PR: Partial remission; RTX: Rituximab

creatinine ratio decrease to 2-3.5 g/24h without re-establishing normal serum albumin levels, a posterior increase in protein-creatinine ratio ought to be faced as resistant disease instead of relapse. Additionally, immunological monitoring in PLA2R1 positive patients may be helpful to distinguish between both situations comparing values at remission and relapse. The same guidelines recommend the use of RTX to manage initial relapse after therapy with either RTX, CNIs or CYP.(34)

In conclusion, in the last decade, RTX has proved to be a safe and effective therapy for primary MN patients, with robust evidence in the subgroup of moderate progression risk.

Table 1 - Overview of clinical trials of rituximab in membranous nephropathy - continued (1)					
Reference	Patients (n)	Main inclusion criteria	Treatment schemes	Main endpoints/outcomes	Results
Ruggenenti et al. 2015 Published in JASN (86)	132	Biopsy proven MN Persistent proteinuria >3.5 g/24h CC >20 mL/min per 1.73 m2 despite optimized treatment without immunossupressants No circulating HBV surface antigents	Weekly 375 mg/m2 RTX infusions for 4 weeks + 1 infusion if > 5 ciculating B-cells were detected 1 week after RTX cessation	% of patients achieving CR or partial NS remission	63.6% of patients achieved CR or partial NS remission at a median follow-up of 30.84 months Lower anti-PLA2R1 antibody titer at baseline (p=0.001) and full antibody depletion 6 months post-rituximab strongly predicted remission (p<0.001)
Dahan et al. 2017 Published in JASN (36)	75 First arm: 38 Second arm: 37	Biopsy proven MN Persistent proteinura >= 3.5 g/24h Albuminemia <30 g/L	First arm: NIAT Second arm: NIAT + RTX (375 mg/m2 two weeks apart)	% of proteinuria reduction at 6 mo; Serum creatinine and GFR variation	35.1% vs 21.1% of patients achieved proteinuria remission at 6 months in the NIAT and NIAT+RTX groups, respectively (p=0.21) Serum creatinine and GFR did not differ between the two groups at month 6 In the NIAT + RTX arm, 56% and 50% of patients achieved immunologic remission at 3 and 6 months In the NIAT group only 4% and 12% of patients achieved the same result at 3 and 6 months

CC: Creatinine clearance; CN: Clinical nephrology; CNI: Calcineurin inhibitor; CR: Complete remission; CYP: Cyclophosphamide; GC: Glucocorticoids; GFR: Glomerular filtration rate; JASN: Journal of American Society of Nephrology; KI: Kidney International; MN: Membranous nephropathy; NE: Nephron Extra; NEJM: New England Journal of Medicine; NIAPT: Non-immunosuppressive anti-proteinuric treatment; NS: Nephrotic syndrome; PLA2R1: Podocyte M-type phospholipase A2 receptor 1; PR: Partial remission; RTX: Rituximab

4.2. Anti-neutrophil cytoplasmic antibody associated vasculitis

AAV includes granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic GPA (eGPA). These conditions are characterized by a necrotizing vasculitis affecting small and medium vessels.(39) Myeloproteinase (MPO) and proteinase 3 (PR3) are

Table 1 - Overview of clinical trials of rituximab in membranous nephropathy - continued (2)					
Reference	Patients (n)	Main inclusion criteria	Treatment schemes	Main endpoints/outcomes	Results
Fervenza et al. 2019 Published in NEJM (37)	130 First arm: 65 Second arm: 65	Biopsy proven MN Proteinuria >5 g/24h CC >= 40mL/min/1.73 m2	First arm: CYP (3.5 mg/kg/d for 12 months) Second arm: RTX (375 mg/m2 two weeks apart)	Composite of CR or PR of proteinuria at 24 months	% of patients had CR or PR in the RTX group and CYP group, respectively (p=0.004) At 24 months, 60% vs 20% of patients had CR or PR in the RTX group and CYP group, respectively (p<0.001) Anti-PLA2R1 antibody decline was faster and of greater duration and magnitude in the RTX group than in the CYP group.
Fernández-Juárez et al. 2020 Published in KI (33)	86 First arm: 43 Second arm: 43	Biopsy proven MN GFR >45 mL/min/1.73 m2 Proteinuria >4g/24h Albuminemia <3 g/dL	First arm: cyclical GC+CYP for 6 months Second arm: Sequential Tacrolimus-RTX	% of patients reaching CR or PR at 24 months	83.7% in the GC+CYP arm and 58.1% in the Tacrolimus-RTX arm achieved CR or PR at 24 months CR was achieved by 60% of patients in the GC-CYP arm compared to 26% in the Tacrolimus-RTX arm at 24 months Median proteinuria decreased from 7.4 g/24h at baseline to 0.35 g/24h at 24 months in the GC-CYP arm and from 7.4 g/24h to 1 g/24 h at 24 months in the Tacrolimus-RTX group (p<0.005)

CC: Creatinine clearance; CN: Clinical nephrology; CNI: Calcineurin inhibitor; CR: Complete remission; CYP: Cyclophosphamide; GC: Glucocorticoids; GFR: Glomerular filtration rate; JASN: Journal of American Society of Nephrology; KI: Kidney International; MN: Membranous nephropathy; NE: Nephron Extra; NEJM: New England Journal of Medicine; NIAPT: Non-immunosuppressive anti-proteinuric treatment; NS: Nephrotic syndrome; PLA2R1: Podocyte M-type phospholipase A2 receptor 1; PR: Partial remission; RTX: Rituximab

neutrophil granule proteins and they constitute ANCAs main target. These antibodies can be found in approximately 90% of patients with small-vessel vasculitis or necrotizing and

Table 1 - Overview of clinical trials of rituximab in membranous nephropathy - continued (3)					
Scolari et al. 2021 Published in JASN (38)	74 First arm: 37 Second arm: 37	Biopsy proven MN Protenuria > 3.5g/d	First arm: 6-month cyclic regimen with GC alternated with CYP every other montth Second arm: 1 g RTX two week apart	Complete remission of proteinuria at 12 months Complete or partial remission of proteinuria at 24 months Occurence of adverse events	At 12 months, 62% receiving RTX and 73% receiving the cyclic regimen had CR or PR Serious adverse events occurred in 19% of patients receiving rituximab and in 14% receiving the cyclic regimen.

CC: Creatinine clearance; CN: Clinical nephrology; CNI: Calcineurin inhibitor; CR: Complete remission; CYP: Cyclophosphamide; GC: Glucocorticoids; GFR: Glomerular filtration rate; JASN: Journal of American Society of Nephrology; KI: Kidney International; MN: Membranous nephropathy; NE: Nephron Extra; NEJM: New England Journal of Medicine; NIAPT: Non-immunosuppressive anti-proteinuric treatment; NS: Nephrotic syndrome; PLA2R1: Podocyte M-type phospholipase A2 receptor 1; PR: Partial remission; RTX: Rituximab

crescentic GN. The remaining 10% of patients are persistently ANCA-negative, but should receive similar treatment.(34)

AAV is a condition that may range from mild to severe in terms of gravity. It is common for severe disease to arise in patients experiencing mild to moderate manifestations over the course of months to years. Early recognition and treatment are of vital significance for reaching outcomes since 30% of patients with renal involvement, the most frequent severe manifestation, can develop ESRD in five years.(39)

Standard treatment approach in AAV includes induction of remission therapy, in the first 3 to 6 months followed by maintenance of remission therapy, for a variable period to prevent relapse.(40) Among drugs such as GC, CYP, mycophenolate mofetil and methotrexate, in the last decades, RTX has gained terrain both as a remission inducer, as well as a therapeutic option to maintain remission in AAV.(39) Nevertheless, it's important to note that many of the studies conducted to establish the efficacy of RTX only included patients with GPA or MPA and excluded patients with eGPA. There are two ongoing RCT's aiming to determine RTX efficacy as a remission inductor(41) and as maintenance therapy in this subtype of patients.(42)

4.2.1. Induction of remission

Remission induction in AAV takes approximately 3 to 6 months to accomplish and is warranted in almost all patients with active GPA or MPA. In the last decade, RTX started to

play a major role in the induction therapy of AAV: in 2011, the use of RTX combined with GC as an alternative to CYP was approved by the FDA in patients with severe GPA or MPA (40,43) and the most recent KDIGO guidelines on GN published in 2020, recommend that GC in combination with CYP or RTX be used as initial treatment of new-onset AAV.(34,44)

The choice between RTX and CYP depends on other clinical aspects: patients with severe renal involvement, with serum creatinine > 4 mg/dL at diagnosis, should be treated with CYP alone, or in association with RTX. On another hand, children, adolescents, pre-menopausal women/man concerned with fertility, frail old patients, and patients in which GC sparing is beneficial, should be considered for RTX (figure 2).(34)

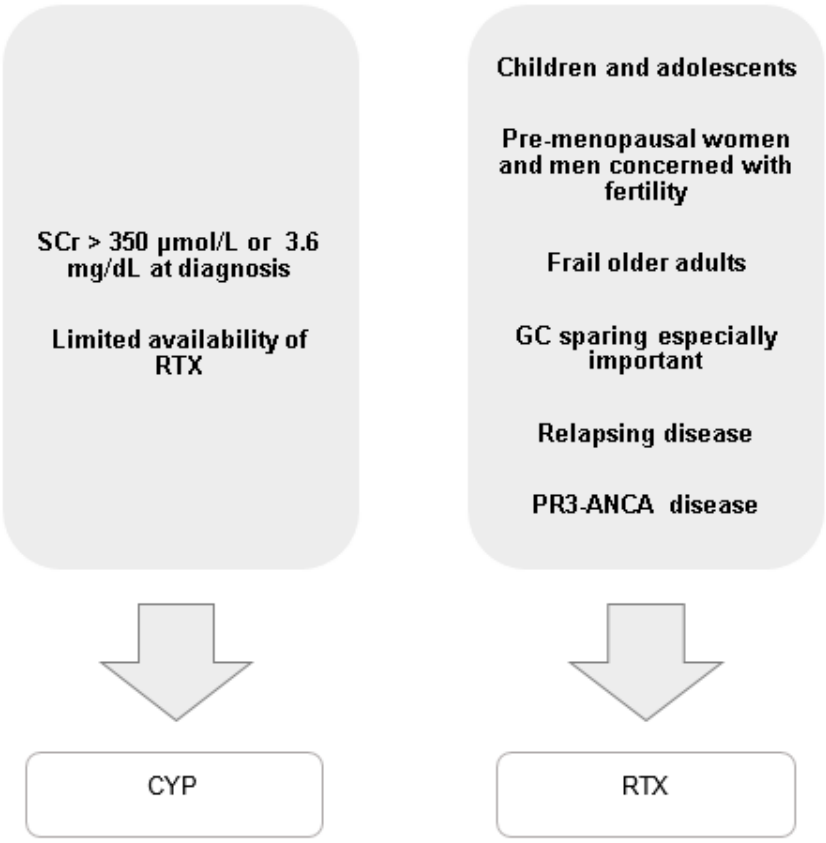

Figure 2 - Considerations to assist choosing CYP or RTX for induction therapy in AAV (adapted from 2020 KDIGO clinical practice guidelines on glomerular disease.(34)
AAV: Anti-neutrophil cytoplasmic antibody associated vasculitis; CYP: Cyclophosphamide; GC: Glucocorticoids; PR3-ANCA: Proteinase 3-anti-neutrophil cytoplasmic antibody; RTX: Rituximab; SCr: Serum creatinine.

The RTX for AAV (RAVE) trial was a randomized, placebo-controlled, multicentre, non-inferiority trial that was published in 2014 in the New England Journal of Medicine. It randomized 197 patients with GPA (75%) and MPA (25%) to RTX (375 mg/m2 per week for four weeks) or oral CYP (2 mg/kg per day). Half the patients had a relapsing disease. The

primary endpoint of remission induction with GC tapering by 6 months was similar for RTX and CYP (64% vs 53%, p>0.05).(45)

A sub-analysis of the 100 patients with relapsing disease, showed that RTX was superior to CYP in remission induction (67% versus 42%, p<0.01) and 47% vs 24% achieved ANCA negativity at 6 months (p<0.05).(45) In a post hoc analysis, the response of PR3 positive patients with severe AAV who were treated with RTX was found to be superior at 6 months (65% vs 48%, p=0.04) but this difference disappeared at 12 and 18 months. In MPO positive patients, the rate of remission induction did not differ between the two groups in any of the time points. In both groups, the rate of adverse events was comparable.(46) It should be highlighted that patients with severe renal dysfunction (creatinine >4 mg/dL) and those with alveolar haemorrhage requiring ventilatory support were excluded, meaning that the efficacy comparison of this drugs in such conditions is uncertain.(45)

Another RCT, RTX versus CYP in AAV (RITUXVAS), conducted in 2015, enrolled 44 patients with de novo AAV and renal involvement. One group received GC + RTX followed by 2 CYP pulses (n=33) and another other group was given GC plus IV CYP for 3-6 months followed by azathioprine (AZA) (n=11). Equivalent remission rates were reported at 6 months in the two arms of the trial (76% vs 82%, p>0.05), reinforcing that RTX is non-inferior to CYP in remission induction. Regarding the primary composite outcome of death, ESRD and relapse, there were no differences between the two groups at a 24 months interval.(47)

Another therapeutic approach that has been less documented is the association of RTX and CYP for induction of remission. Only small observational trials have reported the use of triple therapy with RTX, CYP and GC, showing similar remission rates and in one report, a non-significantly higher mortality rate.(48)

4.2.2. Maintenance of remission

After attainment of remission with induction immunosuppressive therapy, almost all patients are switched to a maintenance regimen. The subgroup of PR3-ANCA positive patients has a higher risk of relapse, so maintenance therapy is even more important.

For maintenance of remission therapy, KDIGO 2020 recommends either RTX or AZA plus low-dose steroids after induction of remission with CYP. For patients with RTX induction,

maintenance should be maintained with RTX, without oral steroids or oral immunosuppressants. For both options, the optimal duration of therapy is unknown, but should be at least for 18 months after induction of remission.(34)

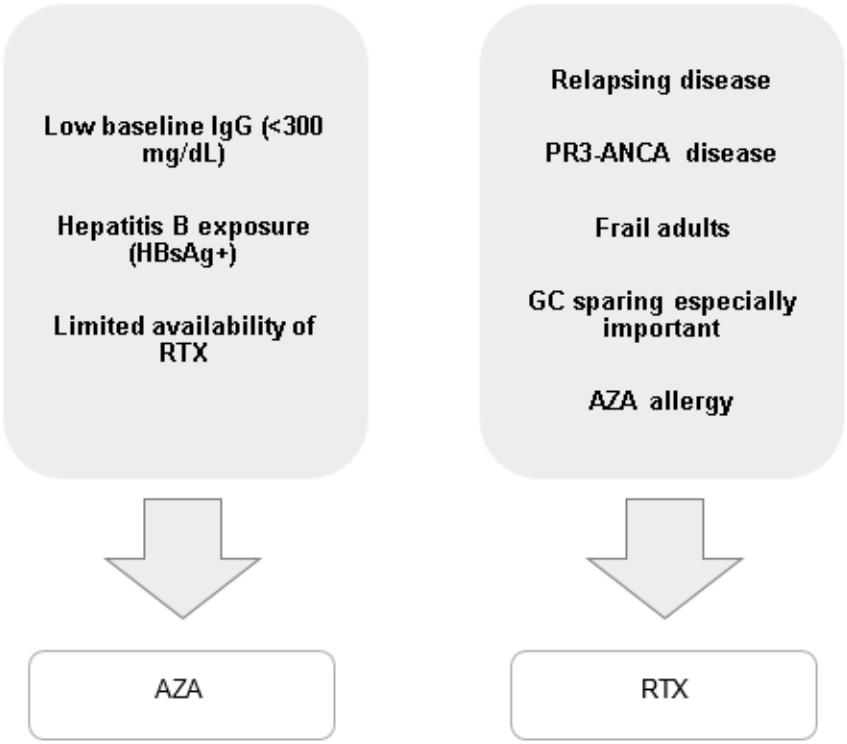

Figure 3 - Considerations to assist choosing AZA or RTX for maintenance therapy (adapted from 2020 KDIGO clinical practice guidelines on glomerular disease.(34)
AAV: Anti-neutrophil cytoplasmic antibody associated vasculitis; AZA: Azathioprine; GC: Glucocorticoids; HBsAg+: Positive for hepatitis B surface antigen; PR3-ANCA: Proteinase 3-anti-neutrophil cytoplasmic antibody; RTX: Rituximab.

When selecting an appropriate treatment option, we should consider initial presentation of disease, patient co-morbidities and relapse risk (figure 3). Among factors that rise the chances of relapse we can find GPA phenotype, PR3-ANCA disease, lower serum creatinine at diagnosis, more extensive disease, ear, nose and throat disease, history of relapse, increased levels or persistence of ANCA at the switch to maintenance therapy and lower cumulative dose of CYC exposure.(40,49)

The most relevant studies of RTX as a maintenance of remission therapy in AAV are summarized next.

The RTX versus AZA for maintenance in AAV (MAINRITSAN), was the first RCT that enrolled 115 patients with newly diagnosed or relapsing GPA, MPA or renal-limited AAV and

compared RTX to AZA for remission maintenance after induction with a GC-CYP regimen. Patients either received 500 mg of RTX with an interval of two weeks and at 6, 12 and 18 months after entering the study or daily AZA for 22 months (2 mg/kg/day for 12 months followed by 1.5 mg/kg/day for 6 months and, lastly, 1 mg/kg/day for the last 4 months). After 28 months of follow up, the following results were achieved: 3 patients (5%) vs 17 patients (29%) had major-relapse in the RTX and AZA groups, respectively (p=0.002). The rates of adverse events were similar in both groups (44/58 events in the AZA arm and 45/57 events in the RTX arm).(50) A follow-up of the MAINRITSAN trial reported relapse-free survival rates of 49,4% vs 71,8% in the AZA and RTX groups, respectively (p=0.003). Patients who received RTX treatment had 12.6 more months without relapse or toxicity compared with patients who had been administered AZA (p<0.001).(51)

The RTX vasculitis maintenance study (RITAZAREM) is a currently ongoing RCT comparing RTX and AZA efficacy to maintain remission only in patients with relapsing disease for a minimum period of 36 months after induction of remission with RTX. 170 patients were randomized in two groups with a 1:1 ratio. The AZA group was given 2 mg/kg/day and the RTX arm received 1000 mg every 4 months for a total of 5 doses. The results of follow up 24 months after the beginning of the trial and 20 months after introduction of maintenance therapy showed that 11/85 (13%) patients experienced relapse in the RTX arm against 32/85 (38%) in the AZA group, revealing superiority of RTX in relapse prevention (p<0.001). Additionally, rates of major relapses and adverse events where higher in the AZA group compared with RTX group (38% vs 18% and 36% vs 22%, respectively).(52)

The question of whether it is better to treat patients with a standardized regimen or an individually tailored one eventually came up after RTX proved to be a successful remission maintenance therapy. The MAINRITSAN 2 trial has shed some light in what might be the best treatment strategy. This RCT has included 162 patients with de novo or relapsing GPA or MPA in complete remission after induction therapy. The control group arm has received the same posology as in the MAINRITSAN trial, 500 mg of RTX on days 0 and 14 and every 6 months until month 18 after the first administration. All 81 patients in the tailored-infusion arm were given 500 mg of RTX at randomization. Patients in this arm had ANCA and CD19+ lymphocytes assed every 3 months and would receive an additional 500 mg of RTX if ANCA titters were different from the previous control or CD19+ counts exceeded 0/mm^3. This trial did not report a significant difference in relapse rate between the two groups at 28 months (p=0.22). 13 patients had 14 relapses in the tailored-infusion arm (17.3%) and 8 patients relapsed in the standard regimen arm (9.9%). Nevertheless, there was a considerable difference in the number of administrations given in both arms, 248 in the tailored-infusion

group and 381 in the fixed regimen group, with medians of 3 (2-4) against 5 (5-5) infusions.(53) This may have implications in terms of choosing treatment regimen options, given that a decreased number of infusions represents a lower quantity of total RTX exposure with no significant difference in relapse rate.

MAINRITSAN 3 and the maintenance of AAV remission by intermittent RTX dosing (MAINTANCAVAS/NCT02749292) are RCTs that are aiming to determine what is the best strategy for remission maintenance treatment on the long term.(54,55)

In 2020, MAINRITSAN 3 study has concluded that extending maintenance therapy with biannual 500 mg RTX administrations past 18 months could lower the incidence of relapses compared to maintenance therapy. This RCT included 97 patients with either GPA or MPA divided in two groups. 96% of patients in the RTX group achieved the primary endpoint, relapse-free survival at 28 months, against 74% in the control group (p=0.008). The only patient relapsing in the RTX group had a minor-relapse, whereas in the placebo group 6 patients had major relapses. No significant difference was found in the rate of adverse events between both groups.(54)

The ongoing MAINTANCAVAS study is comparing whether it is more effective to infuse 2x1000 mg of RTX spaced 2-3 weeks apart in patients with B-cell reconstitution or in patients with serologic ANCA flare. Patients enrolled in this study have been treated with RTX for maintenance therapy for a minimum period of two years.(55) Analyses of data from both MAINTANCAVAS and MAINRITSAN 3 may have the potential for refining maintenance treatment strategies with RTX on the long term.

RTX also has an important role in relapsing disease, and the KDIGO 2020 guidelines recommend that patients with relapsing disease (life- or organ-threatening) should be reinduced, preferably with RTX.(34)

4.3. Lupus nephritis

SLE is a chronic systemic autoimmune disease characterized by clinical heterogeneity, flares and unpredictable course. Autoantibodies and immune-complex deposition are responsible for tissue damage in multiple organs causing significant morbidity and increased mortality. LN is a severe manifestation of SLE and occurs in about 50% of patients with SLE. Risk factors for the development of LN are younger age, male sex and non-European ancestry.

This are also risk factors for more severe LN and progression to end-stage renal disease, which occurs in 10% to 30% of patients with LN.(56)

Mortality associated with SLE is significantly higher in those with LN and death directly attributable to kidney disease occurs in 5% to 25% of patients with proliferative LN. Treatment of patients with LN and the achievement of complete response is of extreme importance, considering the incidence in younger ages and the association with morbidity and mortality.(56,57)

Different treatment strategies are recommended according to LN class and are well defined in KDIGO 2020 guidelines. However, renal outcomes in LN remain suboptimal and multiple promising therapies have failed in clinical trials. Considering SLE pathophysiology, being an immune-complex dependent disease, RTX arises has a promising therapy for these patients.

Even though RTX doesn't represent a first line treatment option, it can be considered for specific patients. The 2019 EULAR recommendations for the management of LN advise 1000 mg of RTX two weeks apart to be used as an alternative or in addition to initial therapies in class III, IV or V in patients presenting active non-responding/refractory disease.(58) The American College of Rheumatology and the 2020 KDIGO guidelines on glomerular disease also agree on using RTX in such situations.(34,59) The main source of evidence for RTX in LN are open-label observational studies showing response rates ranging from 50% to 80% and a meta-analysis including 31 papers that reported 51% of patients achieving complete response and 34% reaching partial response with RTX therapy.(34,60)

The first RCT to approach RTX as a LN treatment was the efficacy and safety of RTX in patients with active proliferative LN (LUNAR) trial. This double-blind RCT aimed to assess RTX's safety and efficacy in patients with active proliferative LN. The trial included 144 patients with class III/IV LN treated with GC and mycophenolate mofetil and then randomized to placebo or 1 g of RTX at baseline, at 15 days, and then at 24 and 26 weeks. Although RTX's arm reported a higher rate of complete and partial remission, no significant difference was observed compared to the placebo arm after 12 months (p=0.18).(61) RTX patients presented greater reduction in anti dsDNA titters and larger improvement in complement levels when compared to placebo. LUNAR had some limitations including the election of unrealistic endpoints for RTX to achieve significant differences, the excessive background immunosuppressive treatment and selection of non-refractory patients. It can take up to 2

years for patients to establish complete renal remission and the percentage of patients who reach it in the short-term is small to moderate.(59)

For patients with refractory LN, the largest report included 22 patients with focal or diffuse proliferative LN who had persistent disease activity despite treatment with a variety of immunosuppressive drugs, such as CYP, MMF, cyclosporin and AZA. RTX was added to the existing immunosuppressive regimen at a dose of 0.5-1 g at day 1 and day 15. At three months post RTX, five patients presented complete response and seven patients had a partial response defined as a >40% improvement in renal parameters.(62)

RTX was also assessed in a series of 20 patients with diffuse proliferative or membranous LN, with resistant or relapsing disease. Fifteen patients had been previously treated with CYP. RTX was given at a dose of 375 mg/m2 weekly for four week and ten patients received additional doses of RTX as maintenance therapy. At a mean follow-up of 22 months, 5 of the 15 patients with diffuse proliferative LN achieved complete response, and five patients had a partial response.(63)

Furthermore, RTX has been used as an attempt to avoid long GC exposure in LN patients. In 2013, a prospective observational study suggested that oral GC exposure could potentially be avoided using two IV infusions of 1000 mg RTX and 500 mg of methylprednisolone two weeks apart followed by maintenance treatment with mycophenolate mofetil. The trial of RTX and mycophenolate mofetil without oral steroids for LN (RITUXILUP) used only IV methylprednisolone, without any oral GC in combination with RTX and mycophenolate mofetil to treat 50 patients with active LN and reported 86% remission rate at 52 weeks. However, these promising results were followed by the premature termination of the RCT due to lack of recruitment.(64)

The existing evidence for RTX is based on observational evidence with small sample sizes and the LUNAR RCT has several handicaps that need to be assessed.

The RTX for LN with remission as a goal (RING) trial (NCT01673295) is a RCT set to evaluate RTX efficacy in achieving complete renal response in patients with LN that have persistent proteinuria superior to 1 g/day despite being subject to standard care for a minimum period of 6 months. It will follow enrolled patients for a period of 104 weeks. Hopefully, results from this trial will give us stronger evidence on RTX use in LN.(65)

Future directions of LN treatment with RTX are based on the association of RTX with belimumab, an anti-B-lymphocyte-stimulator antibody that inhibits the B-cell activating factor. The synergic B-cell depletive effect of these two drugs may be highly effective in eliminating circulating and tissue-resident autoreactive B lymphocytes. RTX plus CYP followed by belimumab for the treatment of LN (CALIBRATE) trial and the study to evaluate the efficacy and safety of belimumab administered in combination with RTX to adult subjects with SLE (BLISS-BELIEVE) are two RCTs that have been planned to investigate this hypothesis.(66,67)

CALIBRATE enrolled 43 patients with recurrent or refractory LN. One arm was treated with RTX plus CYP and GC followed by belimumab infusions once a week for 4 years and the other group received RTX and CYP. While the belimumab group achieved a lower percentage of B cells ($p=0.0012$), total and autoreactive naïve B cells at week 48 ($p=0.0349$), this study did not report any significant benefit from the addition of belimumab to a RTX plus CYP regimen in terms of efficacy ($p=0.452$).(66)

The currently ongoing BLISS-BELIEVE is evaluating the efficacy and safety of belimumab followed by a single cycle of RTX in SLE patients. 200 patients are divided in 3 arms. The first arm will be administered weekly 200 mg of belimumab for 52 weeks plus a placebo at weeks 4 and 6. The second will receive the same posology of belimumab plus 1000 mg of RTX at weeks 4 and 6. Finally, the third arm will be administered belimumab plus standard care for a period of 104 weeks. The proportion of patients with disease control at week 52 constitutes the primary endpoint. Clinical remission after 64 weeks and proportion of patients with disease control after 104 weeks represent the major secondary endpoints.(67)

4.4. Minimal change disease

MCD is a podocytopathy that represents 10% to 15% of idiopathic NS in adults. The pathogenesis of MCD is poorly understood: T-cells dysregulation has been considered to play a major role, but growing evidence suggests that B-cell depleting drugs are effective in the management of MCD.(34)

The KDIGO 2020 guidelines on glomerular diseases recommend an initial treatment of MCD high-dose oral GC (1 mg/kg/day) for initial treatment of MCD. This recommendation is based on low-quality evidence, since contrary to studies in children, most of the evidence for adult patients is from few RCTs with a small number of participants and various limitations and biases. The role of RTX in adult MCD is restricted to patients with contraindications to steroids or in patients with frequently relapsing or GC-dependent MCD, in order to decrease long term

exposure to GC.(34) However, even for these group of patients, the recommendation for RTX is limited and other drugs such including CYP, calcineurin inhibitors or mycophenolic acid analogs, are initially preferred. Evidence suggesting RTX effectiveness in this settings is not very strong.

A meta-analysis from 2020, aimed to determine treatment outcomes of RTX in adult patients with MCD and FSGS, reported an overall remission rate of 80.3% in patients with MCD after RTX therapy based on data from eleven studies (N=170). Patients were followed for 27.6±13.5 months and achieved a complete remission rate of 74.7% and a partial remission rate of 5.6%. There was no significant difference in remission or relapse rates between different RTX dosages (≥ 1500 mg/m^2 vs <1500 mg/m^2). Despite this favourable results, it's important to consider that all studies included in this meta-analysis were observational.(11)

The NEMO study enrolled 10 children and 20 adults with MCD or FSGS who had frequent relapses but were in remission for at least 1 month. 28 participants received 1 dose of RTX and 2 patients were infused with two doses (375 mg/m^2). At the end of the follow-up period of one year, all patients were in remission and the number of relapses decreased approximately 5-fold compared to the year preceding RTX treatment. 18 participants did not need any further maintenance therapy and 15 never relapsed. Compared to the previous year, the medium number of relapses per-patient decreased from 2.5 to 0.5 ($p<0.001$). This reduction was significant across MCD and FSGS patients ($p<0.01$). Additionally, there was a significant decrease in the medium steroid maintenance dose (0.27 mg/kg to 0 mg/kg) and in the medium cumulative dose to achieve relapse remission (19.5 mg/kg to 0.5 mg/kg) with *p* values inferior to 0.001. The observation period was extended to 2 years before and after introducing RTX with similar results.(68) Data from this study suggests that RTX may be efficient in decreasing the burden of immunosuppressive therapies in this type of patients while decreasing the number of relapses and maintaining remission for prolonged periods.

In two prospective studies with frequently relapsing or GC-dependent MCD patients, RTX was able to decrease GC and other immunosuppressive drugs exposure with good results.(69,70) In the first study, 25 participants were infused a single dose of 375mg/m^2 of RTX biannually for a period of 24 months. The total number of relapses 24 months before and after the first dose of RTX was compared and a significant reduction in relapses was reported (108 vs. 8, $p<0.01$). Only 4 patients required GC 24 months after RTX vs 25 at baseline ($p<0.001$), and at a much lower dose.(69) The second study enrolled 15 young adults who were administered two 1 g doses of RTX 6 months apart. There was a significant reduction in the medium frequency of relapses (2.60± 0.28 to 0.4± 0.19, $p<0.001$). Finally, the median GC-

free survival after the first RTX infusion was 25 months (4-34 months).(70) In both studies, most of relapse cases occurred simultaneously with the recovery of B-cell count.

These studies are not very encouraging for the use of RTX in MCD but data from ongoing RCTs is essential to further establish the role of RTX in this pathology. There are at least 3 RCTs currently being held with the aim to establish the efficacy and safety of RTX in MCD and FSGS. The use of RTX in the treatment of nephrotic GN (TURING) trial is a RCT enrolling 112 patients with relapsing or de novo MCD or FSGS and comparing the safety and efficacy of using GC alone to RTX plus GC.(71) RTX from the first episode of idiopathic NS (RIFIREINS) is a RCT comprising 98 patients with a first episode of MCD and is aiming to compare the efficacy of GC vs RTX in remission maintenance.(72) Finally, NCT03298698 will compare prolonged therapy with RTX to high-dose GC in patients with MCD or FSGS unresponsive to 2 months of prednisolone in high-doses.(73)

4.5. Focal Segmental Glomerulosclerosis

The 2020 KDIGO guidelines on glomerular disease recommend high-dose oral GC (1 mg/kg/day) as the 1st line treatment in primary FSGS.(34) The role of RTX is not well established but it may become a useful tool for patients with GC-resistance, GC-dependence or GC contraindication. As in MCD, there is little evidence to support RTX in primary FSGS.

The NEMO trial included 8 patients with FSGS. As previously mentioned, all patients were able to achieve remission at 1 year. RTX was also able to reduce the per-patient medium number of relapses from 2.5 to 0.5 ($p<0.001$) during follow-up.(68) Despite the favourable results, this study was not randomized and had a small sample size.

A recent meta-analysis analysed 51 patients from five studies presenting with FSGS. Participants were followed by a mean time of 18.7±9 months. After treatment with RTX, complete remission was achieved in 42.9% patients and partial remission was reported in 10.7% of patients. In this study, 46.4% did not achieve any type of remission, suggesting that RTX was not very efficient. Also, 47.3% of patients treated with RTX relapsed within this time period, which means that only a small percentage maintained remission. Nevertheless, this results should be interpreted with caution, not only because of the small sample, but also because there was no direct comparison to standard or concomitant treatment. It is also worth mentioning that the burden of NS was not equal across studies and that mild disease may have a better outcome in response to RTX.(11)

The ongoing RCTs (TURING; RIFIREINS and NCT03298698)(71–73), mentioned above, aim to assess RTX's efficacy and safety in patients with MCD and FSGS and will provide us with further important data.

4.6. Immunoglobulin A nephropathy

IgAN is the most common pattern of primary glomerular disease worldwide and remains as a leading cause of CKD and kidney failure. The clinical presentation of IgAN is very heterogenous but a vast majority of patients present with asymptomatic haematuria.(74) For these reason, the management of IgAN in 2020 KDIGO guidelines on GN focus mainly in non-immunosuppressive therapy such as rigorous blood pressure control and lifestyle modifications. However, a small number of patients are at high risk of progressive CKD, despite maximal supportive care, defined as proteinuria >1 g/24h after 90 days of optimized supportive care. In these patients, immunosuppressors might be considered, with a six month course of GC therapy. The role of RTX in IgAN is not established and even for rapidly progressive GN, the KDIGO guidelines refer there is insufficient evidence to use RTX.(34)

There's preliminary observational data suggesting a potential benefit for RTX in IgAN.

In a retrospective cohort study, 22 adult patients with contraindications for GC therapy or refractory/relapsing IgAN were followed for a median of 24 months. 15 patients received 1 g of RTX two weeks apart and 7 were infused 375 mg/m^2/week for 4 weeks. Remission was achieved in 90.9% of patients (most within six months of therapy), although 35% relapsed. Additionally, there was a significant decrease in parameters including 24h-proteinuria, C-reactive protein and prednisone dose among the participants. Overall, RTX was well tolerated and no major adverse effects were found.(75) Results from this study, however, do not represent high-level evidence. A small sample size, the retrospective nature of the study and the fact that many patients had concomitant treatments represent important limitations.

A retrospective analysis of 8 children with chronic GC-dependent IgAN treated with RTX reported a significant reduction in the number of hospitalizations and in median oral GC dose, Seven of the children met the remission criteria defined in the respective study and no relevant adverse events were reported.(76) RTX achieved favourable results in this cohort, but the sample size was small, no standardized approach was used to administer RTX and the retrospective nature of the study as well as the fact that the population didn't include adult patients remain as limitations.

Currently, there is an ongoing RCT, biologics in refractory vasculitis (BIOVAS), aimed to evaluate biologic therapy with infliximab, tocilizumab and RTX against placebo in 140 patients (children and adults) with refractory primary IgAN.(77)

4.7. Hepatitis C Virus-associated cryoglobulinemic glomerulonephritis

HCV infection stands as the most common cause of type II/mixed cryoglobulinemic GN (78) HCV is responsible for expanding B-cell population through chronic stimulation leading to wide-spread auto-antibody synthesis. Through its mechanism of action, RTX has the potential to deplete CD20/CD19+ lymphocytes, thereby decreasing the synthesis of cryoglobulins and, consequently, the deposition of immune-complexes.(79) The KDIGO 2018 guidelines on the treatment of HCV related kidney disease, recommend RTX as the first line therapy in patients with histologically active HCV associated glomerular disease who do not respond to antiviral therapy, particularly those with cryoglobulinemic kidney disease.(80)

RTX has shown to be superior to standard treatment (CYP, GC, AZA, methotrexate and plasma exchange) in two RTCs enrolling patients suffering from HCV associated cryoglobulinemic vasculitis to whom previous antiviral therapy was contraindicated or had failed to induce disease remission. (79,81)

One of the RCT's followed 24 patients with similar disease activity and organ involvement at baseline for a period of 12 months. The control group (n=12) received standard therapy and the other group (n=12) received 375 mg/m^2 of RTX once a week for 4 weeks. The primary endpoint, remission at 6 months was achieved by 83.3% in the RTX group and only by 8.3% in the control group ($p<0.001$), showing that RTX was significantly more effective at inducing remission. RTX was well tolerated among participants.(79)

The second RCT enrolled 59 patients which were assigned to a non-RTX group, receiving either GC, AZA or CYP, or to a RTX group, receiving 1 g of the drug on days 0 and 14. There was a significantly higher proportion of patients who continued their initial therapy at 12 months (primary endpoint) in the RTX group (64.3%) compared to the control group (3.5%). The same results were reported at 3 months (92,9% vs 13.8%, $p<0.0001$), 6 months (71.4% vs 3.5%, $p<0.0001$) and 24 months (60.7% vs 3.5%, $p<0.0001$). RTX was superior in the treatment of 3 target organ manifestations (skin ulcer, GN and peripheral neuropathy). The rate of serious adverse events was similar between both groups.(81)

Results from both studies reported that RTX was safe and effective in this kind of patients but it is important to consider that only 25 of the 83 participants involved in this studies had GN.(79,81)

A prospective study, published in 2018, aimed to evaluate the very long-term effects of RTX use in 31 patients with severe mixed cryoglobulinemia, of which 16 had renal involvement. RTX was administered once a week for 4 weeks plus a dose 1 month and 2 months later (4 plus 2 protocol). From the 2nd month after RTX introduction, serum creatinine levels and 24-hour proteinuria started to decrease (from 2.1 ± 1.7 to 1.5 ± 1.6 mg/dl, $p \leq 0.05$ and from 2.3 ± 2.1 to 0.9 ± 1.9 g/24h, $p \leq 0.05$, respectively), showing a significant improvement of the cryoglobulinemic nephropathy. RTX was well tolerated by patients and no major side effects were reported. After a mean time of 31.1 months, 9 patients relapsed but were effectively re-induced with RTX. 75% of patients survived at 6 years with a 60% chance of remaining symptom-free for 10 years without any therapy. This study showed that RTX was safe and effective in the treatment of patients with severe mixed cryoglobulinemia.(82)

4.8. Other glomerulonephritis

Currently, there is no sufficient evidence to make conclusions about RTX's efficacy and safety in other glomerular diseases, although it is possible that this drug may be of use in certain circumstances. RTX has been used in the treatment of some other GN including anti-glomerular basal membrane antibody GN and idiopathic immunoglobulin and complement-mediated GN with membranoproliferative pattern of injury. Considering the rarity of these GN, it is very difficult to conduct RCTs to evaluate RTX's efficacy and safety.

Conclusion

During the last decade, investigation on RTX's potential efficacy and safety for the treatment of several GN achieved remarkable results, even leading to its recommendation as a first line therapy in specific situations. Undoubtedly, MN and AAV were the pathologies where RTX's role has been established with most certainty.

In MN, RTX was included in the KDIGO 2020 guidelines as a first-line therapy for patients at moderate and high-risk of progressive loss of kidney function, whereas in the KDIGO 2012 guidelines it was not contemplated as a treatment option.

Regarding new-onset AAV, in accordance with the KDIGO 2020 guidelines, GC in combination with either CYP or RTX is recommended as initial treatment. In patients with RTX induction, maintenance therapy should continue RTX while for inducted with CYP, either RTX or AZA plus low-dose steroids remain as possible options.

RTX is not a first line therapy in LN, but the 2019 EULAR, KDIGO 2020 and the American College of Rheumatology agree on the use of RTX as an alternative or in addition to initial therapies in class III, IV or V in patients presenting active non-responding/refractory disease.

The KDIGO 2018 guidelines on the treatment of HCV related kidney disease recommend RTX as the first line therapy in patients with histologically active HCV associated glomerular disease who do not respond to antiviral therapy, particularly those with cryoglobulinemic kidney disease.

In the remaining GN, the role of RTX is not well established yet, despite it being used off-label in some circumstances. There are several ongoing RCTs aimed to investigate RTX efficacy and safety compared to standard treatments and placebo which will certainly further establish RTX's role in the treatment of glomerular diseases.

List of abbreviations

AAV	ANCA-associated vasculitis
ANCA	Anti-neutrophil cytoplasmic antibody
ASMase	Acid Sphingomyelinase
AZA	Azathioprine
CYP	Cyclophosphamide
eGPA	Eosinophilic granulomatosis with polyangiitis
EMA	European Medicines Agency
ESRD	End-stage renal disease
EULAR	European Alliance of Associations for Rheumatology
FDA	Food and Drugs Administration
FSGS	Focal segmental glomerulosclerosis
GC	Glucocorticoid
GFR	Glomerular filtration rate
GN	Glomerulonephritis
GPA	Granulomatosis with polyangiitis
HBV	Hepatitis B virus
HCV	Hepatitis C virus
IgAN	Immunoglobulin A nephropathy
IRR	Infusion-related reactions
IV	Intravenous
KDIGO	Kidney Disease: Improving Global Outcomes
LN	Lupus nephritis
MCD	Minimal change disease
MN	Membranous nephropathy
MPA	Microscopic polyangiitis
MPO	Myeloproteinase
NIAPT	Non-immunosuppressive anti-proteinuric treatment
NS	Nephrotic syndrome
PLA2R1	Podocyte M-type phospholipase A2 receptor 1
PR3	Proteinase 3
RCT	Randomized controlled trial
RTX	Rituximab
SLE	Systemic lupus erythematosus
SMPDL-3b	Sphingomyelin phosphodiesterase acid-like 3b

THSD7A	Thrombospondin type 1 domain-containing 7A

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