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Rituximab in adult minimal change disease and focal segmental glomerulosclerosis - What is known and what is still unknown?

Philipp Gauckler[a,*], Jae Il Shin[b,c,d], Federico Alberici[e,f], Vincent Audard[g], Annette Bruchfeld[h,ah], Martin Busch[i], Chee Kay Cheung[j,k], Matija Crnogorac[l], Elisa Delbarba[m], Kathrin Eller[n], Stanislas Faguer[o,p], Kresimir Galesic[l], Siân Griffin[q], Zdenka Hrušková[r], Anushya Jeyabalan[s], Alexandre Karras[t], Catherine King[u], Harbir Singh Kohli[v], Rutger Maas[w], Gert Mayer[a], Sergey Moiseev[x], Masahiro Muto[y], Balazs Odler[n], Ruth J. Pepper[z], Luis F. Quintana[aa], Jai Radhakrishnan[s], Raja Ramachandran[v], Alan D. Salama[z], Mårten Segelmark[ab], Vladimír Tesař[r], Jack Wetzels[w], Lisa Willcocks[ac], Martin Windpessl[ad,ae], Ladan Zand[af], Reza Zonozi[ag], Andreas Kronbichler[a,*], for the RITERM study group

[a] Department of Internal Medicine IV (Nephrology and Hypertension), Medical University Innsbruck, Anichstrasse 35, 6020 Innsbruck, Austria
[b] Department of Pediatrics, Yonsei University College of Medicine, Seoul 03722, Republic of Korea
[c] Division of Pediatric Nephrology, Severance Children's Hospital, Seoul 03722, Republic of Korea
[d] Institute of Kidney Disease Research, Yonsei University College of Medicine, Seoul 03722, Republic of Korea
[e] Nephrology Unit, ASST Spedali Civili di Brescia, Brescia, Italy
[f] Department of Medical and Surgical Specialities, Radiological Sciences and Public Health, University of Brescia, Brescia, Italy
[g] Department of Nephrology and Transplantation, Rare French Disease Centre "Idiopathic Nephrotic syndrome", Henri-Mondor/Albert-Chenevier Hospital Assistance Publique-Hôpitaux de Paris, Inserm U955, Team 21, Paris-East University, 94000 Créteil, France
[h] Department of Renal Medicine, CLINTEC, Karolinska Institutet at Karolinska University Hospital, Stockholm, Sweden
[i] Department of Internal Medicine III, University Hospital Jena, Friedrich-Schiller-University, Jena, Germany
[j] Department of Cardiovascular Sciences, University of Leicester, Leicester, United Kingdom
[k] John Walls Renal Unit, University Hospitals of Leicester NHS Trust, Leicester, United Kingdom
[l] Department of Nephrology and Dialysis, Dubrava University Hospital, Avenija Gojka Suska 6, 10 000 Zagreb, Croatia
[m] Department of Nephrology, University of Brescia, Hospital of Montichiari, Brescia, Italy
[n] Clinical Division of Nephrology, Department of Internal Medicine, Medical University of Graz, Graz, Austria
[o] Département de Néphrologie et Transplantation d'Organes, Centre de Référence des Maladies Rénales Rares, Centre Hospitalier Universitaire de Toulouse, 31000 Toulouse, France
[p] Institut National de la Santé et de la Recherche Médicale, U1048 (Institut des Maladies Cardiovasculaires et Métaboliques-équipe 12), 31000 Toulouse, France
[q] Department of Nephrology and Transplantation, University Hospital of Wales, Cardiff, UK
[r] Department of Nephrology, 1st Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic
[s] Division of Nephrology, Columbia University Medical Center, NY, New York, USA
[t] Service de Néphrologie, Hôpital Européen-Georges Pompidou, Assistance Publique des Hôpitaux de Paris, 75015 Paris, France
[u] Centre for Translational Inflammation Research University of Birmingham Research Laboratories, Queen Elizabeth Hospital, Mindelsohn Way, Edgbaston, Birmingham B15 2WB, UK
[v] Nephrology, Post Graduate Institute of Medical Education and Research, Chandigarh, India
[w] Department of Nephrology, Radboud University Medical Center, PO Box 9101, 6500, HB, Nijmegen, Netherlands
[x] Tareev Clinic of Internal Diseases, Sechenov First Moscow State Medical University, Moscow, Russia
[y] Department of Nephrology, Juntendo University Faculty of Medicine, Tokyo, Japan
[z] University College London Department of Renal Medicine, Royal Free Hospital, London, UK
[aa] Department of Nephrology and Renal Transplantation, Hospital Clínic, Centro de Referencia en Enfermedad Glomerular Compleja del Sistema Nacional de Salud (CSUR), Department of Medicine, University of Barcelona, IDIBAPS, Barcelona, Spain
[ab] Department of Clinical Sciences Lund, University, Skane University Hospital, Nephrology Lund, Lund, Sweden
[ac] Department of Renal Medicine, Vasculitis and Lupus Clinic, Addenbrooke's Hospital, Cambridge University Hospitals, Cambridge, UK
[ad] Department of Internal Medicine IV, Section of Nephrology, Klinikum Wels-Grieskirchen, Wels, Austria
[ae] Medical Faculty, Johannes Kepler University Linz, Altenberger Strasse 69, 4040 Linz, Austria
[af] Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN, USA
[ag] Division of Nephrology, Vasculitis and Glomerulonephritis Center, Massachusetts General Hospital, 101 Merrimac Street, Boston, MA 02114, USA
[ah] Department of Health, Medicine and Caring Sciences, Linköping University, Linköping, Sweden.

* Corresponding authors.
E-mail addresses: philipp.gauckler@i-med.ac.at (P. Gauckler), andreas.kronbichler@i-med.ac.at (A. Kronbichler).

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ABSTRACT

Primary forms of minimal change disease and focal segmental glomerulosclerosis are rare podocytopathies and clinically characterized by nephrotic syndrome. Glucocorticoids are the cornerstone of the initial immunosuppressive treatment in these two entities. Especially among adults with minimal change disease or focal segmental glomerulosclerosis, relapses, steroid dependence or resistance are common and necessitate re-initiation of steroids and other immunosuppressants. Effective steroid-sparing therapies and introduction of less toxic immunosuppressive agents are urgently needed to reduce undesirable side effects, in particular for patients whose disease course is complex. Rituximab, a B cell depleting monoclonal antibody, is increasingly used off-label in these circumstances, despite a low level of evidence for adult patients. Hence, critical questions concerning drug-safety, long-term efficacy and the optimal regimen for rituximab-treatment remain unanswered. Evidence in the form of large, multicenter studies and randomized controlled trials are urgently needed to overcome these limitations.

1. Background

Nephrotic syndrome (NS) describes a clinical condition with heavy proteinuria, hypoalbuminemia, edema, hyperlipidemia and other associated features such as coagulation disorders and acute kidney injury. Minimal change disease (MCD) and primary focal segmental glomerulosclerosis (FSGS) are among the leading causes of primary NS in adults. The overall incidence of these glomerulopathies is very low (0.6–1.8 per 100,000 adults for MCD and FSGS) [1]. Uncertainty exists about the pathogenesis and optimal treatment strategies for MCD and FSGS, especially among adult patients [2]. In this review, we focus on the potential role of rituximab in adult MCD and primary FSGS.

Especially in childhood, the umbrella term idiopathic NS is still often used collectively for primary MCD and FSGS. MCD is the most common cause of idiopathic NS in childhood, accounting for up to 90% of cases. Because of its favorable course and high response rates to oral corticosteroids, renal biopsy is not performed routinely and the disease is thus termed 'steroid-sensitive nephrotic syndrome' in pediatric patients [3]. Prevalence and steroid responsiveness however decrease with age. Consequently, MCD accounts for only 10%–15% of adult patients with idiopathic NS and is associated with a longer time to remission under corticosteroid treatment and a higher risk of acute kidney injury [3,4]. Nonetheless, overall long-term prognosis for adults with MCD is still excellent with remission rates of 75%–90% and a low risk for end stage kidney disease (ESKD) < 5% [5]. The diagnosis MCD implies the absence of glomerular lesions on light microscopy (LM). Immunofluorescence for deposits is usually negative and extensive podocyte foot process effacement is detected by electron microscopy (EM) [3].

Primary FSGS is thought to be an immune-mediated podocytopathy accompanied by a characteristic focal pattern of glomerulosclerosis with five different histologic variants on LM. Similar histological findings on LM are observed in patients with secondary forms of FSGS which are a sign of adaptive glomerular changes due to excessive nephron workload and hyperfiltration [6–8]. In addition to adaptive glomerular changes, the term secondary FSGS encompasses various other conditions such as genetic, virus-associated or drug-induced forms, that often are difficult to distinguish from true idiopathic/primary FSGS and should be managed conservatively, aiming to control blood pressure and proteinuria [6,9]. Hence, establishing the correct diagnosis is crucial for the management of patients and an important hurdle in the recruitment of respective clinical trials. Interpretation of FSGS-studies is complex as mixed cohorts with primary and secondary disease forms are a frequent limitation [10,11]. In the following sections, we focus on primary FSGS (from this point abbreviated by 'FSGS' only) and the potential responsiveness to B cell-depleting therapies. In contrast to MCD, FSGS is generally a progressive disease with a tendency to develop ESKD. The strongest predictor of ESKD is resistance to immunosuppressive therapy and failure to achieve remission, with 5- and 10-year kidney survival rates averaging 65% and 30% among these patients, respectively [12]. Even achieving partial remission is associated with significantly improved kidney survival rates compared to no

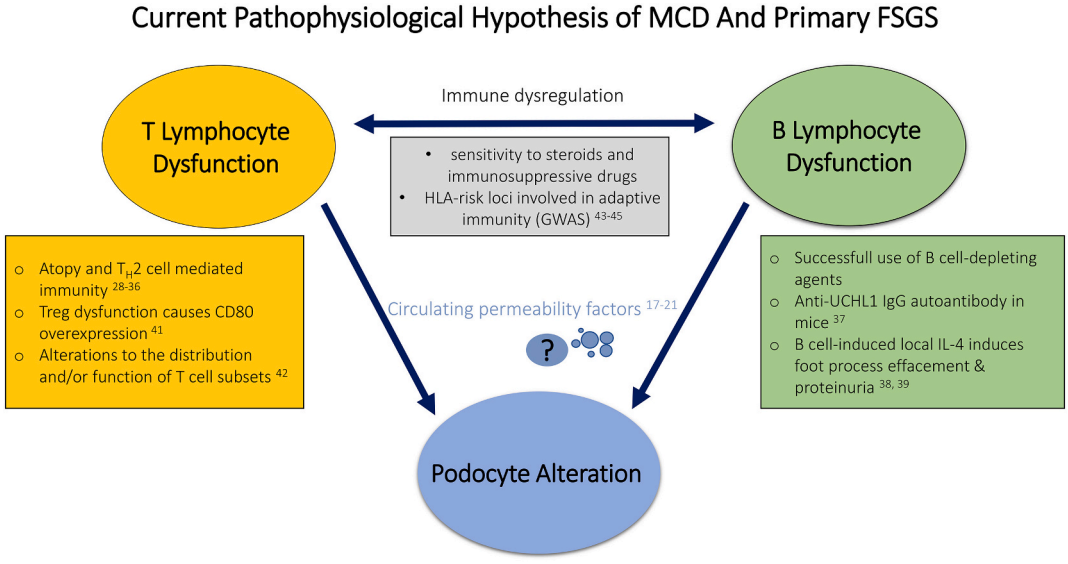

Fig. 1. Pathophysiology of minimal change disease and primary focal segmental glomerusclerosis.
MCD, minimal change disease; FSGS, focal segmental glomerulosclerosis; HLA, human leukocyte antigen; GWAS, genome-wide association studies; T_H2, T helper 2; CD, cluster of differentiation; UCHL1, Ubiquitin Carboxyl-Terminal Hydrolase L1; Ig, immunoglobulin; IL, interleukin.

remission [13,14].

2. Pathophysiology of disease

Historically, both terms are meant to describe two separate disease entities but there is an ongoing debate whether MCD and FSGS may represent one disease continuum with a common pathogenesis and a histological development from MCD to FSGS due to progressive podocyte injury [15]. The underlying mechanism of MCD and FSGS is not fully understood. Initial podocyte injury is regarded to be crucial in the pathogenesis of both MCD and FSGS but several causes are being discussed that might lead to podocyte depletion [6]. As depicted in Fig. 1, a dysregulation of adaptive immunity appears to be central in the pathogenesis of MCD and FSGS. The following section will outline different immunological processes involved.

2.1. Circulating permeability factors

There is some evidence suggesting that the presence of one or more circulating permeability factors that disrupt the podocyte integrity in primary FSGS [16,17]. The strongest clinical support for this hypothesis in FSGS is the high recurrence rate after kidney transplantation of about 30%–40% of patients, which may occur within hours of transplantation [18]. Circulating factors such as soluble urokinase plasminogen activator receptor, cardiotrophin-like cytokine factor-1 and anti-CD40 antibodies have been proposed as potential causative for FSGS but none have been validated and proven for their pathogenic role yet [19,20]. For MCD there is generally less evidence indicating the presence of circulating factors. Nonetheless, clinical observations made in 1974, such as remission induced by measles infection, occurrence of MCD in Hodgkin's disease and clinical response to immunosuppressive therapy, suggest a systemic abnormality of T cell function resulting in the secretion of a circulating factor [21]. The presence of a vascular permeability factor produced by lymphocytes in MCD patients was first described by Lagrue et al. in 1975 [17,22]. Since then various candidates such as the cytokines, interleukin (IL)-8 and IL-13, circulating hemopexin or podocyte-secreted, hyposialated angiopoietin-like 4 have been identified [23–26], but existing data remains inconsistent and unvalidated [17].

2.2. Atopy and eosinophils in the nephrotic syndrome

Involvement of T helper 2 (T_H2) cell-mediated immunity in the pathogenesis of idiopathic NS has been suggested [27]. This hypothesis matches with the frequently described associations between MCD and atopy, as the latter disposition is well-known to be driven by T_H2 cell responses and elevated levels of IgE, IL-4 and IL-13 [28–32]. In children with idiopathic NS, serum levels of IgE and IL-13 correlated with disease activity, independently of atopic co-morbidities suggesting a coincidence of atopy in children with idiopathic NS rather than a causal linkage [31–34]. Peripheral blood eosinophils are another classical diagnostic marker implicated in the pathogenesis of atopic diseases but its role in idiopathic NS is still unclear [35]. We suggest further research should aim at investigating the potential link of eosinophilia with idiopathic NS and the impact on clinically meaningful endpoints.

2.3. Possible contact points with rituximab – B cells and beyond

The role of B cells in the pathogenesis of MCD and FSGS has gained attention, mainly due to the successful use of B cell depleting agents, as further discussed below. This sheds new light on pathophysiological processes involved in these two glomerular diseases. Recently, an IgG-antibody directed against Ubiquitin Carboxyl-Terminal Hydrolase L1 (UCHL1) was shown to cause podocyte detachment and associated with relapses of idiopathic NS in mice [36]. In a murine model, B cells activated locally in the kidney were able to induce glomerular injury and proteinuria by production of IL-4. In contrast, IL-4-deficient B cells did not induce proteinuria, whereas overexpression of IL-4 alone was

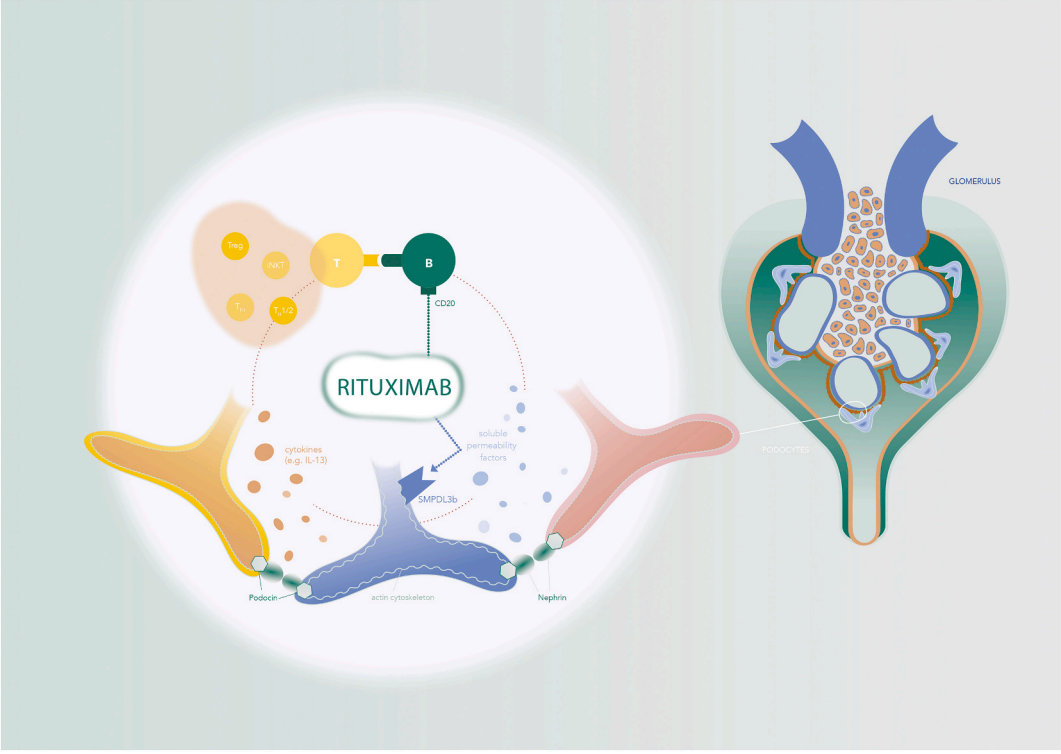

Fig. 2. Possible mode of action of rituximab in patients with minimal change disease and focal segmental glomerulosclerosis.
CD, cluster of differentiation; Treg, T-regulatory cell; iNKT, invariant natural killer T cell; T_{FH}, T follicular helper cell; $T_H1/2$, type 1/2 T helper cell; IL-13, interleukin 13; SMPDL-3b, sphingomyelin phosphodiesterase acid-like 3b.

sufficient to cause foot process effacement and proteinuria. Increased B cell numbers were present in the kidneys of children with FSGS compared with mesangio-capillary glomerulonephritis [37]. In kidney biopsies of patients with MCD, STAT6 activation (induced by IL-4) was increased, suggesting IL-4 exposure in these patients [38]. These observations suggest that B cells are involved in the pathogenesis of MCD and FSGS, possibly by production of cytokines, such as IL-4 [38]. Interestingly, IL-4 is the critical cytokine contributing to the risk of atopy and allergic diseases, triggering Ig class-switch to produce IgE and T cells to $CD4^+$ T_H2 cells [39]. Recently, Shimada et al. postulated a "two-hit" theory to describe the pathogenesis of MCD. Accordingly, cytokines (e.g. IL-13), microbial products or allergens induce a direct stimulation of podocytes leading to the induction of CD80 (also named B7.1) as the initial hit. This causes an alteration of the podocyte structure and increases permeability. Under normal conditions, CD80 expression on podocytes is controlled by T regulatory (Treg) cytokines or production of cytotoxic T-lymphocyte antigen 4 (CTLA-4) and IL-10 by the podocyte itself. Hence, a second hit due to Treg dysregulation or impaired podocyte autoregulation is crucial and leads to sustained podocyte injury and MCD [40]. Modifications of T cell subsets were observed in patients enrolled in a multicenter, double-blind, and randomized trial assessing the efficacy of rituximab compared to a control group in childhood MCD. A decrease of $CD4^+CD25^{high}FoxP3^{high}$ Treg cells was associated with disease relapses, while rituximab-treated patients had a low relapse rate accompanied by a low frequency of CD4 CD8 double negative ($CD3^+CD4^-CD8^-$) invariant natural killer T (iNKT) cells expressing an invariant T cell receptor α-chain (Vα24). Rituximab was shown to specifically reduce the frequency of $CD4^+$ follicular T cells (TFH cells) that drive naïve and memory B cells to differentiate into antibody-secreting cells (see Fig. 1). As relapses are associated with rapid reconstitution of switched memory B cells, the authors conclude that B cell depletion might induce qualitative alterations of TFH cells and thus inhibit reconstitution of switched memory B cells [41]. Recently, genome-wide association studies identified different HLA and non-HLA risk loci involved in adaptive immunity for childhood-onset steroid-sensitive NS, supporting the concept of an underlying immune dysregulation in the disease pathogenesis [42–44].

2.4. A hypothetical mode of action of rituximab in MCD and FSGS

B cells are involved in the pathogenesis of primary MCD and FSGS as illustrated in Fig. 2, and presumably, play more an indirect role, either through production of a circulating factor as proposed mainly for FSGS or by interaction with T cells as described in MCD.

Rituximab, a chimeric, monoclonal IgG1 antibody, exerts its B cell-depleting effects via binding to CD20. Besides direct, cytotoxic effects (complement- and antibody-dependent), a diversity of indirect effects, including lipid raft modifications, kinase and caspase activation and effects on apoptotic/antiapoptotic molecules appear to play a crucial role for the observed variability in response to rituximab treatment [45]. In addition, other B cell-independent mechanisms might be responsible for the antiproteinuric effects of rituximab seen in patients with renal disease. Besides modifying effects on T cell subsets, RTX might also lead to a depletion of a small number of T cells that co-express both CD3 and CD20 (approximately 3%–5% of all circulating T cells), as reported in patients with multiple sclerosis [46]. A direct regulation of podocyte function has been postulated and sphingomyelin phosphodiesterase acid-like 3b (SMPDL-3b) proposed as such target [47]. Notably, while binding of rituximab to SMPDL-3b was shown in previous studies using fixed sample assays, Kim et al. could not reproduce this in an experimental in vivo setting with nonfixed cells [38]. In patients at high risk for recurrent FSGS after kidney transplantation, rituximab treatment was associated with a lower frequency of post-transplant nephrotic range proteinuria compared to historical controls. Additionally, rituximab partially prevented SMPDL-3b downregulation observed in podocytes treated with sera of patients with recurrent FSGS after transplantation [48]. In contrast, a benefit in preventing disease recurrence after transplantation was not confirmed in an observational study [49]. Krüppel-like factor 15, a zinc-finger transcription factor expressed in human podocytes, contributes to mediate the beneficial effects of glucocorticoid therapy via stabilization of the actin cytoskeleton of podocytes in both MCD and FSGS [50]. To date, the relevance of this finding in the discussion of rituximab efficacy is unclear.

3. Immunosuppression in MCD and FSGS

Existing treatment strategies are generally supported by a weak level of evidence as reflected in the current KDIGO Clinical Practice Guidelines for Glomerulonephritis 2012. Evidence is particularly scarce for adult MCD and FSGS, as most available data is derived from clinical trials in children and from observational studies. Supportive measures, such as antihypertensive, antiproteinuric and dietary approaches, are pivotal for all patients with proteinuric glomerular diseases [2]. MCD and FSGS generally show poor response to these measures, thus initial immunosuppressive therapy with corticosteroids is recommended for all patients with clinical features of nephrotic syndrome (evidence grade 1C) [12,51]. Current definitions for NS, complete (CR) and partial remission (PR) and corresponding disease courses are given in Table 1.

Initial response rates to oral glucocorticoid therapy with achievement of CR or PR in up to 75% of adult patients with MCD [4] and remission rates of 40% to 65% in FSGS are reasonable [54,55]. However, complicated disease courses due to i) steroid resistance (SR) (up to 27% in MCD [4], 40%–60% in FSGS [55,56]), ii) relapses after steroid tapering or withdrawal (65%–80% in MCD [5], 30%–70% in FSGS [57]) and iii) frequently relapsing (FR) disease (10%–30% in MCD [5]) are common. Of note, there is an ongoing discussion whether SR exists in MCD or if these patients rather have unsampled FSGS due to the focal nature of the disease [15]. In FSGS, a prolonged initial steroid therapy > 16 weeks appears to be crucial to achieve CR (15% for steroids < 16 weeks versus 61% for steroids > 16 weeks) [58].

Table 1
Definitions of nephrotic syndrome in adult patients [12,52,53].

Steroid-dependent (SD)	Two relapses during or within 2 weeks of completing steroid therapy
Steroid-resistant (SR)	Persistence of proteinuria despite prednisone 1 mg/kg/d or 2 mg/kg every other day for > 4 months
Frequently relapsing (FR)	Two or more relapses within 6 months or four or more relapses within 1 year of achieving remission
Complete remission (CR)	Reduction of proteinuria to < 0.3 g/d or < 300 mg/g (< 30 mg/mmol) urine creatinine and normal serum creatinine and serum albumin > 3.5 g/dl (35 g/L)
Partial remission (PR)*	Reduction of proteinuria to 0.3–3.5 g/d (300–3500 mg/g [30–350 mg/mmol]) urine creatinine and stable serum creatinine (change in creatinine < 25%) or Reduction of proteinuria to 0.3–3.5 g/d (300–3500 mg/g [30–350 mg/mmol]) urine creatinine and a decrease > 50% from baseline, and stable serum creatinine (change in creatinine < 25%) **not seen in minimal change disease*
Nephrotic syndrome (NS)	Heavy proteinuria > 3.0–3.5 g/d or > 3.0 g/g urine creatinine, peripheral edema and hypoalbuminemia < 2.5–3.5 g/dL *(varying definitions in the literature)*

Considering the toxicity of such high steroid doses, such recommendations are still controversial [59]. Conversely, a short-term (2 months) steroid regimen may be an effective treatment option for adult steroid-sensitive MCD patients [60].

Calcineurin inhibitors (CNI), alkylating agents and antimetabolites are commonly used steroid sparing agents in MCD and FSGS. Tacrolimus monotherapy [61] or in combination with low-dose steroids [62] may be an option to a conventional glucocorticoid regimen as initial therapy for adult MCD. Nonetheless, these alternative agents are so far only recommended as second- or third-line agents in adults with FR or SD MCD and FSGS [12,51,59].

Cyclophosphamide, cyclosporine alone or cyclosporin in a steroid-combined regimen have all shown efficacy as first-line therapy in adult patients with SD or FR MCD [63–65]. In a Chinese study including adult patients with SR/SD MCD, tacrolimus was equally effective compared with cyclophosphamide in inducing and maintaining remission and might induce remission more rapidly than intravenous pulse cyclophosphamide [66,67]. Whereas CNIs block T cell activation and stabilize actin directly in podocytes, mycophenolate mofetil has an antiproliferative effect on both B and T cells. In a retrospective review of adult MCD cases by Waldman et al., mycophenolate mofetil was studied as second-line agent in 14 patients (7 SD, 4 SR, 3 partial steroid responders) showing remission in 64% of patients (6/7 SD, 1/4 SR) [4]. A recent multicenter clinical trial found no superiority of a low-dose oral steroid therapy plus mycophenolate mofetil compared with a conventional oral steroid therapy alone after 4 weeks of treatment, at least for the first episode of MCD [68].

In FSGS, one randomized controlled trial (RCT) showed that cyclosporin in combination with low-dose prednisone is superior to prednisone alone in preserving renal function and achieving CR or PR [69]. However, the active treatment period with cyclosporin was only six months in this study and relapses were common after remission, occurring in 60% of remitters by week 78 [69]. Another five-year follow-up study showed higher remission rates of cyclosporin with prednisolone (85.7%) compared to azathioprine with prednisolone (80%) and prednisolone alone (62.5%) [54]. Tacrolimus monotherapy might be another option as first-line therapy for adult FSGS [70]. The efficacy of mycophenolate mofetil alone compared to steroids has never been tested. One RCT compared a 12-months course of cyclosporin to a combination of oral pulse dexamethasone and mycophenolate mofetil in 93 children and 45 young adults with SR FSGS and used six primary outcome levels of proteinuria response. No difference was seen in achieving PR or CR in the first year (primary outcome) in both, adults and children. Nevertheless, good outcome levels (level one to three) were achieved in 45.9% of cyclosporin treated and 33.3% in the combined dexamethasone/ mycophenolate mofetil group. Additionally, there was no significant difference in maintaining remission for 26 weeks after cessation of treatment (main secondary outcome) among the two subgroups [71]. As the study was underpowered and secondary forms of FSGS were likely included, results may be interpreted cautiously [72]. One open label randomized pilot study from India compared the efficacy (measured end point was change in urinary protein/ creatinine ratio) of mycophenolate mofetil in combination with prednisolone to prednisolone alone. After 6-months, the mycophenolate mofetil-based regimen was as effective as steroids alone but remission was induced faster and steroid exposure could be reduced [73]. Additional treatment with chlorambucil in combination with steroids showed a lack of efficacy in a RCT [74]. In complicated disease courses, including SD, SR or FR FSGS, the same agents have been evaluated in a few randomized and observational studies [55]. One RCT compared tacrolimus and cyclophosphamide, both in combination with prednisone, in adult patients with SR or SD FSGS and showed similar efficacy of both regimens. Six- and twelve-month remission rates were 67% and 73% in the tacrolimus-group, compared with 56% and 67% in the cyclophosphamide-group [75]. Other immunosuppressive agents have been tested in small trials or case series such as levamisole, mizoribine, tumor necrosis factor-α inhibitors, pirfenidone, fresolimumab, saquinivir and sirolimus [6] and the results have been reviewed elsewhere [57].

Each of the described steroid sparing agents has major disadvantages. CNI and antimetabolites show frequent relapse rates after withdrawal in both MCD and FSGS [76]. CNI lead to nephrotoxicity with prolonged use and serum levels need to be monitored tightly whereas mycophenolate mofetil has dose-dependent effects on the gastrointestinal system and bone marrow [3]. Alkylating drugs like cyclophosphamide are very efficient but have major toxic side effects including infertility, urotoxicity and oncogenicity [77]. Neoplastic complications of alkylating drugs may occur years or even decades after treatment exposure [78]. Thus, most trials may have underestimated the true number of malignancies attributable to the treatment and thus the malignancy risk of these agents. In view of the availability of modern, effective and well tolerated drugs these limitations argue for alternatives in the management of MCD and FSGS.

4. Rituximab

Rituximab is approved for the treatment of non-Hodgkin's lymphoma, rheumatoid arthritis (RA) and ANCA-associated vasculitis (AAV) by the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA). Beyond that, rituximab is increasingly used off-label in various autoimmune diseases, including myasthenia gravis, systemic lupus erythematosus, idiopathic thrombocytopenic purpura and Sjögren syndrome [79].

4.1. Safety

In these indications, rituximab showed a favorable long-term safety profile [80]. Infusion-related reactions are frequent, manifesting as an immediate hypersensitivity reaction. A pooled analysis of patients with RA reported infusion-related reactions in about 25% of patients during the first infusion with less than 1% of cases considered as serious [81]. Thus, pretreatment with paracetamol, antihistamines and corticosteroids is recommended [80]. Hepatitis B virus (HBV) reactivation in HBsAg-negative/ HBcAb-positive patients following rituximab has been reported and can be prevented by HBV-screening and antiviral prophylaxis [80]. Severe infectious complications, such as *Pneumocystis jirovecii* pneumonia (PCP) and progressive multifocal leukencephalopathy (PML) due to reactivation of JC virus are rare but potentially fatal complications, mainly described among patients with lymphoproliferative disorders and concomitant or previous exposure to other immunosuppressive agents [80,82]. To our knowledge, no case of PML has been reported in patients treated with rituximab monotherapy. Given the fact that rituximab treatment often allows tapering or withdrawal of other immunosuppressants, the true risk of severe infections attributable to rituximab is unclear [83]. Infectious complications are typically reported in patients with pre-existing immune defects, significant comorbidities or concomitant intense immunosuppression [84]. Among patients with RA, the overall serious infection rate was 4.31 per 100 patient-years [81]. A slightly higher risk was found among 370 patients with various autoimmune diseases, with a rate of serious infections of 5.3 per 100 patient-years during rituximab therapy [85]. Importantly, infection rates vary between indications, an observation that may be at least partly explained by different steroid-regimes. A higher infection rate is seen in patients with AAV, as shown in the landmark trials RAVE and RITUXVAS [86–88]. In RITUXVAS, 21.2 serious infections per 100 patient-years were seen [87]. Reported rates in observational studies are even higher and trimethoprim-sulfamethoxazole prophylaxis should be considered in these patients [89,90]. In contrast, low infection rates are reported in patients with NS. In a retrospective analysis of 24 adult patients who received rituximab for membranous nephropathy (n = 11), MCD (n = 7), FSGS (n = 4) and membranoproliferative glomerulonephritis (n = 2) only one single serious infection (1.6 per

100 patient-years) was reported (bronchopneumonia), but fully recovered after a course of antibiotics [91]. NEMO, a prospective off-on trial, evaluated the effects of rituximab in 10 children and 20 adults with MCD, mesangial proliferative glomerulonephritis and FSGS. After one year of follow-up 5 serious infections were observed in the adult subgroup (25 per 100 patient-years). At the time of infection, all patients were still receiving concomitant immunosuppressive treatment and all fully recovered [92]. In contrast, no serious infectious complications were observed in a number of studies [93–98]. Non-uniform reporting of serious infectious complications may explain these differences and information from RCTs are expected to inform about the true infectious risk of rituximab in these diseases. A detailed overview of infectious complications is provided in supplementary Table 1 (see supplementary appendix).

Hypogammaglobulinemia and late-onset neutropenia are two other side effects associated with rituximab [80]. Patients with nephrotic syndrome might be at particular risk for persistent hypogammaglobulinemia and, in children, low IgG levels at baseline appear to increase the risk [99,100]. Thus, monitoring levels of immunoglobulins after rituximab application may be informative, especially in patients with recurrent infections, to identify the actual risk of hypogammaglobulinemia in these patients and potentially predict the infection risk.

Long-term data evaluating the malignancy risk after rituximab in renal disease is scarce. A retrospective study analyzing the malignancy risk of 323 patients with AAV over a mean follow-up of 5.6 years showed that rituximab-treated patients had a lower malignancy risk than cyclophosphamide-treated patients. Notably, rituximab was not associated with an increased malignancy risk in patients with AAV compared with the general population [101]. In the above-mentioned safety-study by van den Brand et al., three blood malignancies and five solid cancers (two of them fatal) were observed and possibly related to the combined therapy of an alkylating agent (cyclophosphamide or chlorambucil) with corticosteroids during a period of 40 months follow-up of patients with membranous nephropathy. In comparison, 2 solid cancers were observed in the rituximab-group and assessed as unrelated to treatment by physicians directly in charge of the patients [102]. Corresponding long-term follow-up data for rituximab in MCD and FSGS is not available. To address this appropriately, studies with a follow-up period of 60 months or longer are needed.

4.2. Dosing

4.2.1. Initial dosing

The optimal initial dosing of rituximab for off-label indications remains unknown. A classic four-dose protocol consisting of 4 weekly doses of 375 mg/m^2 of body surface area is used for hematologic indications, whereas a regimen of 2 applications of 1 g fixed-dose two weeks apart is used in RA. For adults with MCD or FSGS the optimal initial dosing remains unknown. Different dosing protocols (375 mg/m^2 of one to four weekly doses or 1 g once or on day 1 and 15) were used in subgroups of a few retrospective studies [93–95,97,103,104] and 3 prospective trials [92,96,105]. Here, either no correlation was found between the different treatment protocols [93,94] or no conclusions could be made because of the small size of the treated subgroups [95]. There is some evidence that even a single-dose of rituximab (375 mg/m^2) may be effective to induce remission and reduce relapse rates in adult MCD and FSGS [92,105]. Larger, controlled trials are urgently needed to allow comparisons between different dosing protocols in MCD and FSGS.

4.2.2. Subsequent dosing

Rituximab usually persists in the circulation for 3 to 6 months, followed by recovery of B cells to pretreatment levels by 12 months [106]. In patients with nephrotic range proteinuria however, drug half-life is shortened due to urinary loss of rituximab [80]. Correspondingly, lower rituximab levels were reported in proteinuric patients with membranous nephropathy compared to non-proteinuric patients with RA who received the same dosing regimen [107]. Hence, a shorter half-life of rituximab among patients with NS may require respective adaptions in rituximab-dosing [108]. In MCD and FSGS, the optimal

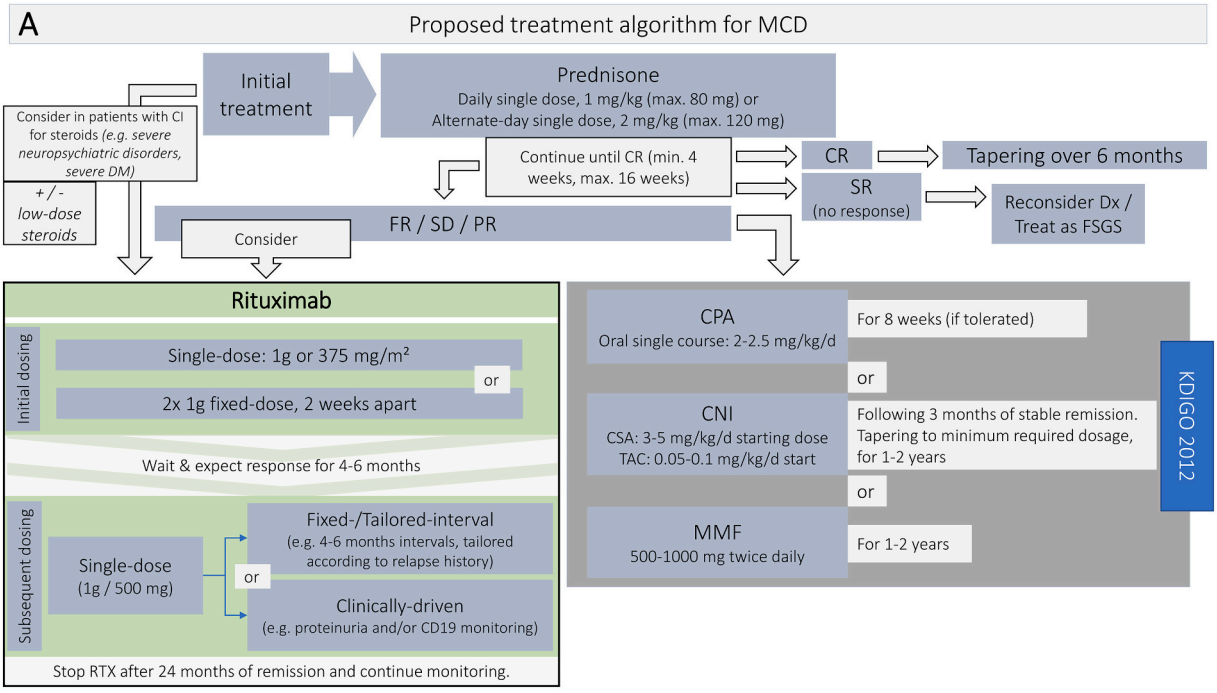

Fig. 3. Proposed algorithm for the application of rituximab in minimal change disease.
MCD, minimal change disease; CI, contraindication; DM, diabetes mellitus; CR, complete remission; SR, steroid-resistance; Dx, diagnosis; FSGS, focal segmental glomerulosclerosis; FR, frequently relapsing, SD, steroid-dependent; PR, partial remission; CPA, cyclophosphamide; CNI, calcineurin inhibitors; CSA, cyclosporin A; TAC, tacrolimus; MMF, mycophenolate mofetil; CD, cluster of differentiation; RTX, rituximab.

timing and dosing of rituximab-reapplication to either maintain remission or in disease relapse are not known. After B cell depletion, re-emergence begins with $CD19^+$ transitional B cells, thus measuring $CD19^+$ B cells was proposed for monitoring rituximab-treatment in RA [109]. Another rationale supporting CD19-monitoring was a masking-effect of CD20 antigen upon rituximab-binding. However, this could not be confirmed ultimately [110] and additional evidence exists that rituximab might interfere with CD19 expression as well [111]. Although B cell reconstitution after rituximab is associated with a certain risk for disease recurrence, remission may last despite complete B cell recovery and relapses can occur in the presence of sustained depletion of B cells [112–115]. Hence, B cell recovery after rituximab appears to be an unreliable marker to predict relapses in patients with NS [116]. Delayed reconstitution of switched memory B cells may be useful to predict relapses in those patients [116]. Additionally, an increase in the $CD4^+/CD8^+$ T cell ratio after rituximab was observed but no association with the individual relapse risk could be drawn [116].

Currently, no guideline exists for the use of rituximab in MCD and FSGS. A possible treatment algorithm how and when rituximab may be applied in these entities is provided in Fig. 3 for MCD and Fig. 4 for FSGS.

4.3. Efficacy

Treatment with rituximab, despite the paucity of efficacy data, changed the therapeutic landscape in both diseases. While reduction/withdrawal of steroids and concomitant immunosuppression was possible in most cases, relapse rates remained low and were significantly reduced compared to time periods before rituximab administration. Retrospective studies with long term follow-up provided evidence that relapse free survival can be achieved in the long run, which argues for an immunologic switch at least in some patients. Table 2 provides an overview of trials investigating the efficacy and safety of rituximab in MCD and FSGS. Respective RCTs for this indication are limited to pediatric studies.

Less evidence supports the use of rituximab in adult patients with MCD or FSGS. A long-term follow-up of 16 adult patients with SD/SR/FR MCD treated with rituximab together with steroids showed CR in 13 patients enabling discontinuation or tapering of steroids. At a median follow-up of 44 months, 8 patients remained in remission and relapses occurred in 7 patients with re-application of rituximab in 4 of these, while one patient had no response to therapy [103]. In another retrospective analysis of 17 adult patients with SD/FR MCD, rituximab treatment led to a significant reduction of relapses per year ($1.32 +/- 0.85$ to $0.16 +/- 0.21, p < 0.05$) and tapering of concomitant steroid therapy [93]. In this study, relapse rates were lower in patients who received rituximab in remission compared to those not in remission (20% and 57%, respectively). In NEMO, total relapses decreased from 88 to 22 during one year of follow-up, compared with the year before RTX application. The steroid maintenance dose per patient decreased from a median of 0.27 mg/kg to 0 mg/kg ($p < 0.001$). The effects were significant across all subgroups (children, adults, MCD and FSGS) [92].

A retrospective study of the Spanish GLOSEN registry compared 50 adult patients with SD/FR NS treated with steroids rituximab in combination with another immunosuppressant. While 28 patients received additional rituximab treatment, 22 patients served as control group. CR was achieved in 82% in the rituximab group versus 63% in the control group. The relapse rate per year before and after rituximab application was significantly reduced ($p < 0.001$) and additional immunosuppressants to achieve sustained remission were lower in the rituximab group than in the control group. The baseline relapse rate before rituximab treatment was significantly higher in the rituximab group than in the control group, thus a direct comparison between the groups was not possible [94]. Guitard et al. evaluated 41 adults with MCD receiving rituximab in a multicenter retrospective study. Overall response, defined as remission of NS and withdrawal of at least one immunosuppressant, was achieved in 78%. In the median follow-up period of 39 months, relapses occurred in 18 responders (56%). Of these, 17 received a second course of rituximab leading to clinical response. 9 patients had sustained remission even after B cell recovery [95]. In 2014, we analyzed available study data (14 studies) of adult patients ($n = 86$) with SD/FR MCD ($n = 77$) or FSGS ($n = 9$) regarding relapses before and after rituximab treatment. Treatment with rituximab reduced the number of relapses per year from 1.3 (0–9) before

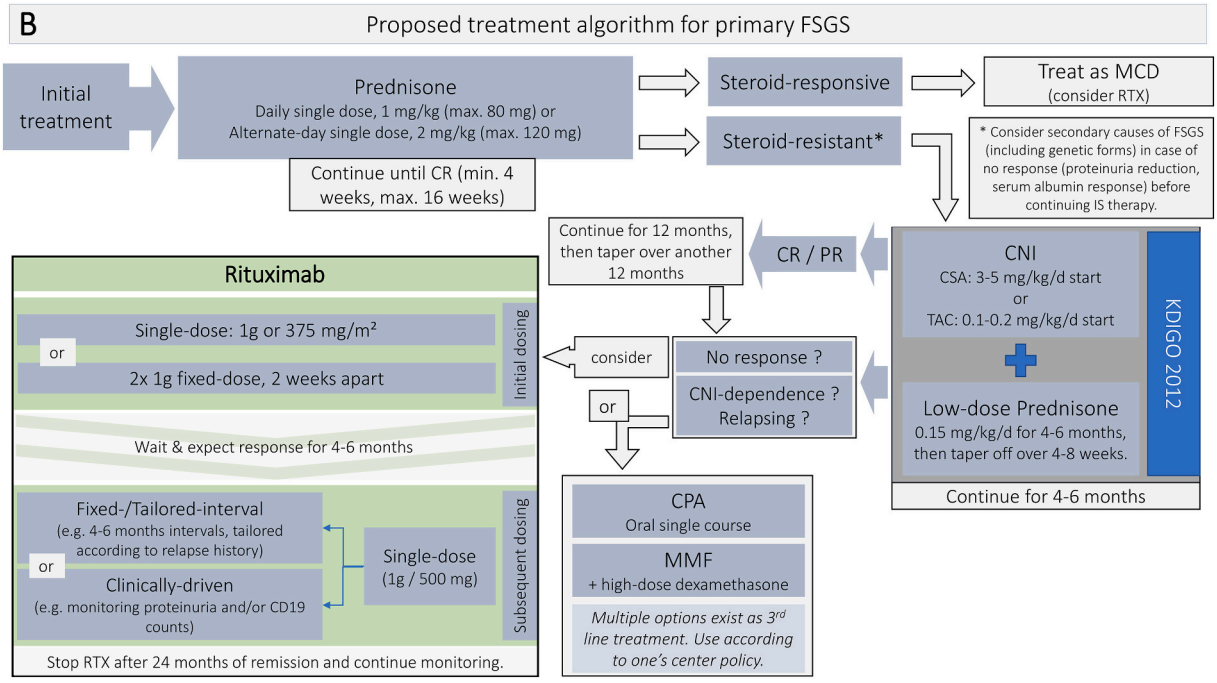

Fig. 4. Proposed algorithm for the application of rituximab in primary focal segmental glomerulosclerosis.
FSGS, focal segmental glomerulosclerosis; CR, complete remission; MCD, minimal change disease; RTX, rituximab; IS, immunosuppressive; CNI, calcineurin inhibitors; CSA, cyclosporin A; TAC, tacrolimus; PR, partial remission; CPA, cyclophosphamide; MMF, mycophenolate mofetil; CD, cluster of differentiation.

Table 2
Overview of studies of rituximab in minimal change disease and focal segmental glomerulosclerosis in adults.

First author, (study)	Year	Design	Patients	RTX / Immunosuppression	FU	Proteinuria	Relapse
Bruchfeld [103]	2014	Retrospective	16 adults, SD/SR/FR MCD	RTX (different regimes) + CS +/− RTX re-application	44 months (median, 12–17)	Initial CR ± PR: 93.8% CR ± PR at end of FU: 50%	RR at end of FU: 43.8%
Munyentwali [93]	2013	Retrospective	17 adults, SD/FR MCD	RTX (different regimes) +/− RTX re-application	29.5 months (median, 5.1–82)		RR: 39%; Reduction of RR per year: from 1.32 +/− 0.85 before to 0.16 +/− 0.21 after RTX ($p < 0.05$)
Ruggenenti, (NEMO) [92]	2014	Prospective, multicenter, off-on	10 children, 20 adults, SD/FR MCD, MesGN, FSGS	RTX (single-dose or 2 × 375 mg/m^2)	12 months before and after RTX		Number of relapses: 22 after RTX versus 88 before RTX RR after RTX: 70% in children versus 40% in adults 54.5% in MCD/MesGn versus 37.5% in FSGS
DaSilva [94]	2017	Retrospective, multicenter (GLOSEN registry)	28 (RTX) + 22 (control) adults, SD/FR MCD/MesGN ($n = 42$) / FSGS ($n = 8$)	CS + additional IS +/− RTX		CR: 82% (RTX) versus 63% (control)	Reduction of RR per year: 1.1 +/− 0.63 versus 0.01 +/− 0.02 ($p < 0.0001$) RR after RTX: FSGS > MCD ($p = 0.02$)
Guitard [95]	2014	Retrospective, multicentre	41 adults, SD/FR MCD	RTX (different regimes) +/− RTX re-application +/− additional IS	39 months (median, 6–71)	CR: 61%, PR: 17%	RR: 56% of responders; median time to relapse: 18 months (3–36)
Roccatello [96]	2017	Prospective	8 adults, FSGS (complex)	High-dose RTX (8 weekly 375 mg/m^2)	29.1 months (median, 24–42)	Non-significant reduction from 5.3 ± 1.9 g/day before to 3.9 +/− 1.8 g/day after RTX	
Fernandez-Fresnedo [97]	2009	Retrospective, multicenter (GLOSEN registry)	8 adults, SR FSGS	RTX (different regimes) +/− re-applications; several IS prior and concomittant to RTX	16.4 months (mean, 12–24)	Non-significant reduction from 14.0 +/− 4.4 g/d before to 10.5 +/− 4.9 g/d after RTX	
Colliou [104]	2019	Retrospective, multicentre	23 adults (≥ 60 years), MCD/FSGS; (out of 116 total)	RTX alone (n = 1), + CS ($n = 21$), + CNI ($n = 1$)	34 months (median, 11.8–56.5), (total patients)	CR: 14/23 (61%), PR: 4/23 (17%)	RR: 7/23 (30%); Median time to relapse: 13 months *(no differentiation of mixed cohort possible)*
Ramachandran [98]	2019	Prospective, singlecentre; (RTX to maintain remission)	24 adults (17–48 years), SD/SR MCD ($n = 11$)/FSGS ($n = 13$) with CNI-dependence	RTX 1 × 375 mg/m^2 +/− additional low-dose (100 mg); +/− additional IS	12 months	Overall-CR: 54%, -PR: 25% MCD-CR: 100% FSGS-CR: 38%, -PR: 38% SD-CR: 93%, -PR: 7% SR-CR: 22%, -PR: 44%	RR: 8/24 (33%) Median time to relapse: 7 months

SD, steroid-dependent; SR, steroid-resistant; FR, frequently relapsing; CS, corticosteroid; RTX, rituximab; CR, complete remission; PR, partial remission; FU, follow-up; RR, relapse rate; MesGn, mesangial proliferative glomerulonephritis; IS, immunosuppressants; CNI, calcineurin inhibitor.

rituximab to 0 (0–2) after rituximab ($p < 0.001$), while proteinuria decreased from 2.43 (0–15) g/day to 0 (0–4.89) g/day ($p < 0.001$), respectively [117]. Of note, the number of patients with FSGS included in this study was small (n = 9) and all were steroid-responsive.

Roccatello et al. reported results of eight patients with FSGS having major risk factors precluding corticosteroids or conventional immunosuppression who received high-dose rituximab (8 weekly doses of 375 mg/m^2) and were prospectively followed up for a minimum of 2 years. Only one patient showed an improvement of proteinuria and renal function while 7 patients did not respond and had persistent proteinuria in nephrotic range [96]. The low response rate might be attributed at least partially to a high number of secondary forms of FSGS among the cohort, as the included patients were comparably old with a high rate of co-morbidities and heterogenous biopsy characteristics (only 2 out of 8 patients showed widespread podocyte foot process effacement). Similar negative findings were reported from the GLOSEN registry. Of eight patients with SR FSGS and previous failure of at least one additional immunosuppressant, only three showed a positive influence of rituximab [97]. In a recent retrospective multicenter study of older patients (≥ 60 years) receiving immunosuppressive therapy for MCD/FSGS, rituximab induced CR or PR in 18 out of 23 individuals [104]. In a recent prospective single-centre study from India, 24 patients (mean age 24.29 years, 17–48) with SD/SR MCD ($n = 11$) or FSGS ($n = 13$) and CNI-dependence, rituximab was used to maintain remission. All patients were in CR or PR at the time of rituximab -administration. After 12 months, patients with MCD and SD NS had excellent outcomes with CR occurring in 100% and 93% respectively, while patients with FSGS or SR NS could maintain CR in only 38% and 22% respectively [98]. Considering the complexity of the study population (dependence to CS and CNI) and the study design (rituximab use for maintenance treatment), comparisons of these results with other studies are limited. It should be emphasized that several of the presented studies have significant limitations, mainly due to mixed cohorts of patients with MCD and FSGS or patients diagnosed as idiopathic NS without further differentiation. Furthermore, reported patients had varying previous treatment modalities and response definitions, declared as SD, SR, or FR. Presumably, a proportion of patients diagnosed as SD/SR/FR FSGS actually exhibit an underlying secondary cause of disease and therefore show no response to any immunosuppressive agent.

Currently, three controlled trials have been initiated independently in order to assess the efficacy and safety of rituximab in adult MCD and FSGS. TURING (EudraCT: 2018–004611-50) is a randomized, double-blind, placebo-controlled trial investigating safety and efficacy of rituximab in combination with steroids to steroids alone in 112 patients with relapsing or newly diagnosed MCD or FSGS. RIFIREINS (NCT03970577) is a French multicenter trial of 98 adult patients with a first episode of MCD comparing the efficacy of rituximab versus steroids to maintain remission. Lastly, a smaller open-label RCT (NCT03298698) will compare continued treatment with high-dose prednisone to treatment with rituximab in adult patients with MCD/FSGS unresponsive to 8 weeks of high-dose prednisone.

Taken together, rituximab appears to be a promising strategy for FR/SD MCD to reduce relapse rates and corticosteroid exposure, although the evidence is still limited. The efficacy data in patients with FSGS are conflicting so far.

5. Conclusion

NS in adults due to MCD or FSGS is a heterogenous disease complex with a highly variable clinical course. Current treatment strategies are based on supportive, antiproteinuric measures and immunosuppressive agents such as steroids, alkylating agents and CNIs. Steroid-dependence/resistance or frequent relapses require prolonged drug exposure resulting in high rates of adverse events attributable to these drugs [118]. B cells are involved in the pathogenesis of MCD and FSGS, giving a rationale for a targeted therapy in both entities. While efficacy and safety of rituximab are shown for several autoimmune-mediated diseases, clinical data supporting its use in MCD and FSGS is still limited. Consequently, rituximab is still a second line treatment option for these entities, reserved for patients with a complex disease course or with contraindication for first-line agents. Several ongoing RCTs will hopefully provide evidence-based data in the upcoming years. Until then, several questions related to the use of rituximab in these patients remain unanswered [119]. Drug-safety and long-term efficacy, the optimal regimen for rituximab-application, prediction of relapses after rituximab and the role of peripheral blood eosinophils in adult MCD and FSGS are central issues that we aim to address with RITERM, a multicenter, international, retrospective study.

Author contributions

PG and AK designed the study. PG wrote the first draft of the manuscript. All other co-authors critically revised the manuscript, carried out major modifications and approved the final version.

Declaration of Competing Interest

VA reports grants from ADDMEDICA, outside the submitted work; AB reports consulting fees from Chemocentryx, from Merck/MSD and from Astra Zeneca, outside the submitted work; MB reports lecture fees from Boehringer Ingelheim, from Bristol-Myers Squibb, from Novartis, travel support from Hexal, lecture fees and travel support from Vifor Fresenius and lecture fee from Servier, outside the submitted work; CKC reports grants from GlaxoSmithKline, grants and consultancy fees from Retrophin, outside the submitted work; SF reports lecture fees from VIFOR Pharma, outside the submitted work; CK reports being funded by National Institute for Health Research (NIHR) as academic clinical fellow (ACF), during the conduct of the study. All the other authors declared no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.autrev.2020.102671.

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