SMGroup

Biologic Drugs Treatment in Glomerular Disease and Renal Transplantation: An Update

Maurizio Salvadori[1]*, Giuseppina Rosso[2] and Elisabetta Bertoni[1]

[1]Department of renal transplantation, Careggi University Hospital, Florence, Italy

[2]Division of Nephrology, San Luca Hospital, Lucca, Italy

***Corresponding author:** Maurizio Salvadori, Department of renal transplantation, Careggi University Hospital, viale Pieraccini 18, 50139 Florence, Italy, Tel: +39-55-597151; Fax: +39-55-597151; Email: maurizio.salvadori1@gmail.com

Published Date: May 25, 2016

ABSTRACT

Glomerular diseases and renal transplantation share common pathogenetic pathways in determining renal injury. In the last years biologic drugs appeared to be powerful agents able to target specific cells or specific molecules, so to exhibit peculiar actions. Aim of this review has been to update the state of art of biologic drugs in renal diseases and in renal transplantation documenting the functional capabilities for each agent to be used both in some glomerular disease and in renal transplantation. For a better understanding biologic agents have been divided according their capability to target: innate immune system; B cell network; T cell network; systemic inflammation. All the agents to date used in randomized controlled trials according ClinicalTrial.gov have been properly cited and reported with their identifiers. To date the majority of biologic agents has been documented to act in both conditions, some only in glomerular diseases and some only in renal transplantation. Studies are ongoing to check also for the latter agents the efficacy in both clinical conditions. New biologic agents are still at the horizon and further randomized controlled trials will clarify their utility.

INTRODUCTION

In the past, glomerular diseases and renal transplantation have always been considered as independent fields of nephrology. This concept has been supported by the prevalent rate of antibody production and immune complexes formation in glomerulonephritis versus the direct action of immune cell in renal transplantation [1]. Recent findings have shown that the pathogenetic mechanisms operating in both conditions share common pathways that offer new therapeutic approaches identical for both conditions.

METHODS

We have analyzed the available data on complement and renal diseases and renal transplantation by careful revision of the currently available data. Literature research was performed using PubMed (NCBI/NIH) under employment of the search terms "complement cascade", "complement and glomerulopathies", "dense deposit disease", membranoproliferative glomerulonephritis", C3 glomerulonephritis", "complement and renal transplantation", "targeting complement", "eculizumab". Studies currently under way were sought for in "clinicaltrials.gov" and the European EUDRACT register. The papers published in the last three years on international journals on transplantation and kidney disease were carefully examined. Almost 230 papers were selected for this review. Randomized Controlled Trials with results unknown, terminated or withdrawn have been excluded from the study.

In this review, after having described which these common pathogenetic pathways are, we will review in details which are to date the principal biologic medicines adopted in both conditions.

COMMON PATHOGENETIC PATHWAYS

Innate Immune System

The innate immunity acts through the recognition of Pathogen Associated Molecular Patterns **(PAMPs)** or Damage-Associated Molecular Patterns **(DAMPs)** by macrophages, Dendritic Cells **(DCs)**, leukocytes [2,3]. Innate immunity acts on antigen processing, so representing a link to adaptive immunity, favoring the antigen presentation, the T and B cell responses and the specific adaptive immune response [4]. The activation of the innate immunity has been documented in several Glomerulonephritis **(GN)** among which IgA-GN [5-7], crescentic GN, anti-neutrophil cytoplasmic autoantibody-GN (ANCA-GN) [8,9] and lupus GN [10,11].

The complement is another essential component of the innate immune system. Complement involvement has been clearly identified in several renal diseases as lupus GN, Membranoproliferative GN **(MPGN)** and C3GN, and Hemolytic Uremic Syndrome **(HUS)** [12,13]. Its role has recently been recognized in autoimmune GN and ANCA vasculitis [14,15].

Recent studies have documented a pivotal role of the innate immunity also in renal transplantation where it causes two steps damage. Early after transplantation the innate immunity

contributes, principally via the complement activation, to the Ischemia-Reperfusion Injury **(IRI)** [16,17]. Later on, IRI represents a link with the adaptive immunity and may cause Cell Mediated Rejection **(CMR)**, Antibody Mediated Rejection **(ABMR)** and progressive graft injury [18-20].

B cells and Antibody Network

Circulating antibodies are deeply involved in the development of GN as well as in the renal transplantation damage. Circulating antibodies are involved in the pathogenesis of Membranous Nephropathy **(MN)** where they are directed against neutral endopeptidase [21], as well as against other podocyte enzymes as M-type phospholipase-2-receptor [22], aldose reductase and manganese superoxide dismutase [23-25]. Circulating nephrotoxic autoantibodies have also been recognized in ANCA vasculitis [26], in hepatitis C-related cryoglobulinemia [27], in lupus GN [28] and in the anti glomerular basement GN [29].

In renal transplantation a relevant proportion of rejection episodes is mediated by circulating antibodies that, after binding to the antigens of the graft donor cells, cause the ABMR. In addition, the activation of the complement cascade recruits macrophages and neutrophils and causes additional graft injury [30]. Moreover, recent data document the antibody involvement also in antibody mediated chronic rejection where the "bad" activity of antibodies may also be involved in previously considered "chronic" lesions (i.e. transplant glomerulopathy) [31,32].

T cells Network

Several lines of evidence support a role for T cells in the pathogenesis of several GN. T cells are clearly involved in the pathogenesis of ANCA vasculitis [33,34]. In ANCA GN CD4 and CD8 T cells are present within the disease lesions in relationship with Antigen Presenting Cells **(APCs)** and B cells [35].

Similarly, abnormalities in T cells and in T cell activation have been reported in lupus GN [36,37], in anti GBM GN [38] and in IgA GN [39].

Clearly T cells are deeply involved in renal transplantation and the regulation of alloreactive T cells ultimately determines whether the graft is rejected or accepted [40].

Systemic Inflammation

An inflammatory "milieu" and its related cytokines are involved in the pathogenesis of several GN.

Up-regulation of pro-inflammatory cytokines and the efficacy of blocking agents have been documented in Focal Segmental Glomerular Sclerosis **(FSGS)** [41]. Similarly, cytokine network up-regulation has been documented in ANCA GN [42,43] and in lupus GN. In the latter disease newer cytokines have been identified in the pathogenesis [44]. Finally, macrophage up-regulation is also involved in the pathogenesis of the inflammation and its block is under investigation in a safety study for IgA-GN [45].

In renal transplantation the cytokine up-regulation and the increased network of inflammatory factors contributes to cause renal damage [46,47]. A study from Wu et al. [47] allowed identifying the role of several inflammatory proteins in the disease progress. Trials with anti-inflammatory agents are ongoing, but to date their usefulness seems to be related only to the islet transplantation.

The pathogenetic similarities above mentioned, imply similar therapeutical approaches.

Principally in the recent years, the biologic agents have the most important role. The biologic agents are defined as large molecules typically derived from living cells and used in the treatment, the diagnosis or the prevention of the diseases. The biologic medicines have a specific target, are often more than 200 times the size of a small molecule and include therapeutic proteins, DNA vaccines, monoclonal antibodies and fusion proteins.

BIOLOGICS IN RENAL DISEASES AND RENAL TRANSPLANTATION

Targeting the Innate Inflammatory Response and Complement

The main targets related to the innate immune response are DCs, Toll-Like Receptors **(TLRs)**, complement and their biological downstream. The majority of the drugs used or the trials ongoing concern the renal transplantation, with the exception of the drugs targeting complement. Indeed, in the case of renal transplantation, the timing of innate system activation is well known, principally in the case of IRI and the drugs may be timely administered. This happens rarely in the glomerular diseases.

DCs: they have a relevant role in the immune response and additionally, may operate as a link between the innate and adaptive immunity. The Rabbit Antithymoglobulins **(rATG)** inhibit the DCs function [48]. In addition, in a primate model of IRI, the rATG administered prior to reperfusion, resulted in a reduced expression of ICAM-1, platelet endothelial cell adhesion molecules, CD11b and E-selectin [49].

TLRs: Experimental studies documented that the prevention of the activation of the innate immunity may be achieved by inhibiting TLR2, which is expressed on the tubular epithelial cells together with the TLR4. The inhibition of the TLR2 with a new monoclonal antibody might significantly reduce the IRI. A placebo-controlled study to evaluate the safety and efficacy of OPN-305, the monoclonal antibody anti TLR2, in preventing DGF, is now ongoing (NCT01794663) [50].

The inhibition of TLR4 using pharmacological agents might be beneficial in transplantation because of the pivotal role of TLR4 in the IRI and in the associated DGF and allograft rejection [51]. Eritoran is a synthetic lipid A analog that blocks the TLR4 activation. To date no clinical trial is ongoing with eritoran neither in glomerular diseases neither in renal transplantation.

Downstream to TLRs activation, several molecules might represent optimal targets to block the innate immune system activation. Among these molecules NFkB has a peculiar role. A recent study has documented a powerful protection against the renal IRI by the T-cell specific NFkB

inactivation [52]. An up-regulation and translocation of activated NFkB subunits has been detected in several renal diseases as IgA-GN [53] and FSGS [54]. To date no trial is ongoing with biologic drugs inhibiting NFkB.

Complement and complement cascade: are two important targets both in the glomerular diseases and in the renal transplantation.

Indeed, the complement is involved not only in the activation of the innate immune system, but also in the development of several glomerular diseases and in the transplantation injury mediated by the immune cells and by the cytokines.

In the glomerular diseases the activation of the complement cascade is well documented in the atypical HUS, in the Shiga-like toxin producing Escherichia Coli hemolytic uremic syndrome **(STEC-HUS)** and in the Thrombotic Thrombocytopenic Purpura **(TTP)**, in the C3 glomerulopathy, membranoproliferative GN type I, Dense Deposit Disease **(DDD)**, ANCA vasculitis and membranous nephropathy [55].

In renal transplantation, the complement cascade is principally involved in IRI, in the acute and in the chronic ABMR and in the renal fibrosis [56].

Anti C5 biologics

Eculizumab, a fully humanized monoclonal antibody that binds with high affinity to C5 and prevents the generation of Membrane Attack Complex **(MAC)**, has been recently approved for the treatment of aHUS and is in randomized clinical trials (RCTs) for other renal diseases.

To date [57] 13 trials are performed for a HUS and STEC-HUS, 1 trial for MPGN (Table 1). 6 of these RCTs have been completed with results documenting the efficacy of eculizumab in a HUS.

Table 1: Randomized Controlled Trials ongoing with Eculizumab in glomerular diseases.

Rank	Identifier	Status	Study name
1	NCT02093533	Recruiting	Eculizumab in primary MPGN
2	NCT00844545	Completed	Open label controlled Trial of Eculizumab in Adult Patients With Plasma Therapy-Resistant aHUS
3	NCT00844844	Completed	Open label controlled Trial of Eculizumab in Adolescent Patients With Plasma Therapy-Resistant aHUS
4	NCT00844428	Completed	Open label controlled Trial of Eculizumab in Adolescent Patients With Plasma Therapy-Sensitive aHUS
5	NCT00838513	Completed	Open label controlled Trial of Eculizumab in Adult Patients With Plasma Therapy-Sensitive aHUS
6	NCT01194973	Completed	An Open-Label, Multi Center Clinical Trial of Eculizumab in Adult Patients with aHUS
7	NCT01193348	Completed	An Open Label, Multi Center Clinical Trial of Eculizumab in Pediatric Patients with aHUS
8	NCT01755429	Completed	The Safety and Efficacy of Eculizumab in Japanese Patients with aHUS
9	NCT01522170	Enrolling	aHUS Observational Long Term Follow Up
10	NCT01522183	Recruiting	aHUS Registry
11	NCT01770951	Completed	A Retrospective, Observational, Non-interventional Trial to Assess Eculizumab Treatment Effect in Patients with aHUS
12	NCT02205541	Recruiting	Eculizumab in Shiga-toxin Related Hemolytic and Uremic Syndrome Pediatric Patients
13	NCT01410916	Completed	Safety and Efficacy Study of Eculizumab In Shiga-Toxin Producing Escherichia Coli **(STEC-HUS)**
14	NCT01406288	Completed	Completed Outbreak of HUS Linked to Escherichia Coli of Serotype 0104:H4

MPGN: Membrano-Proliferative Glomerulonephritis; **ANCA**: Anti Neutrophil Cytoplasmic Antibody; **aHUS**: Atypical Hemolytic Uremic Syndrome; **STEC-HUS**: Shiga-Toxin Producing Escherichia.

RCTs with eculizumab are also ongoing for kidney transplantation, in particular 6 trials for the prevention or the treatment of acute or chronic ABMR, 2 trials for the prevention of delayed graft function, 1 trial for the prevention of IRI and 1 trial for the prevention of glomerular diseases recurrence after transplantation (Table 2) [58].

The beneficial effect of eculizumab on aHUS has been recently documented by two studies [59,60].

Table 2: Randomized Controlled Trials ongoing with Eculizumab in renal transplantation.

1	NCT01756508	Recruiting	Eculizumab for Prevention and Treatment of Kidney Graft Reperfusion Injury
2	NCT01919346	Recruiting	Eculizumab for Prevention of DGF in Kidney Transplantation
3	NCT02142182	Recruiting	A Trial for Prevention of DGF After Kidney Transplantation
4	NCT01567085	Active	Safety and Efficacy of Eculizumab in the Prevention of AMR in Sensitized Recipients of a Kidney Transplant from a Deceased Donor
5	NCT01095887	Active	Eculizumab Added to Conventional Treatment in the Prevention of Antibody-mediated Rejection in Blood Group Incompatible Living Donor Kidney Transplantation
6	NCT01106027	Active	Dosing Regimen of Eculizumab Added to Conventional Treatment in Positive Crossmatch Deceased Kidney Transplant
7	NCT01895127	Recruiting	Efficacy and Safety of Eculizumab for Treatment of Antibody-mediated Rejection Following Renal Transplantation
8	NCT00670774	Active	Dosing Regimen of Eculizumab Added to Conventional Treatment in Positive Crossmatch Living Kidney Transplant
9	NCT01399593	Active	Safety and Efficacy of Eculizumab to Prevent AMR in Living Donor Kidney Transplant Recipients Receiving Desensitization
10	NCT01029587	Recruiting	Eculizumab to Enable Renal Transplantation in Patients with History of Catastrophic Antiphospholipid Antibody Syndrome

DGF: Delayed Graft Function; **AMR**: Antibody Mediated Rejection.

The eculizumab treatment has also been proven effective for STEC-HUS and for TTP. In particular, the eculizumab effectiveness has been documented in two STEC-HUS outbreaks occurring in Germany and in France [61,62].

The pathogenetic similarities between aHUS and some C3 glomerulopathies might imply that eculizumab treatment could fit well in treating also these diseases. Eculizumab treatment seems to be effective in DDD and in C3GN. To date the eculizumab efficacy for C3 glomerulopathies is limited to 6 case reports [63-68] and the results from a 1-year, open-label study [69].

Complement activation occurs in two phases after transplantation: during reperfusion after that the kidney has undergone a significant period of ischemia and during the acute rejection once the innate and adaptive immune system has recognized the donor antigens. Three RCTs are now active aiming to control the ischemia-reperfusion injury and the consequent DGF (NCT01919346, NCT02145182, NCT01756508) [70]. In addition, eculizumab proved to be effective in treating the recurrence after transplantation of renal diseases with complement activation involvement. Zuber et al [71] successfully treated 22 renal transplant recipients with recurrence of aHUS. Similarly, McCaughan et al [66] reported a patient with DDD recurrence after kidney transplantation successfully treated by eculizumab.

Eculizumab has also been successfully used in reducing antibodies in highly sensitized patients with positive cross-matches prior to transplantation [72-74]. In a large case-control study patients with circulating Donor Specific Antibodies **(DSAs)** were treated with eculizumab after transplantation and compared to the historical controls [75]. In this study, eculizumab was able to significantly lowering ABMR and to decreasing the 1-year transplant glomerulopathy incidence rate. In addition, ongoing studies are testing the efficacy of Eculizumab in preventing long-term graft damage in patients with DSAs. Finally, both the anti C5 mAb and the C5aR antagonists are currently being tested in humans to assess their effects on human alloreactive T cells *in vivo*. The study results will be soon being published (NCT01363388) [76].

Mubodina and ergidina are also anti C5 biologics. Mubodina is a recombinant human monoclonal antibody against C5; ergidina is a second generation minibody endowed with a tail peptide that leads directly towards the target. Both these molecules are still in preclinical phase. No clinical trials are ongoing with these drugs [77].

Anti C5a and C5aR biologics

C5a is a powerful anaphylatoxin that stimulates the cytokine production, enhances the T cell activation and augments the leukocyte adhesion and the vascular permeability. In transplanted kidneys with IRI or acute rejection as well as in some glomerulonephritis there is an increased expression of the C5aR. Recently, Cravedi et al [78] documented that pharmacological C5aR blockade in mice reduces the graft versus host disease, prolongs the survival rate and inhibits the T cell responses. Several therapeutic agents targeting the C5a and the C5aR axis are in different stages of clinical development ranging from preclinical studies to phase II studies. These agents may target the axis at different levels, from conversion of C5 to C5a and C5b, to inactivation of C5a, or to the inhibition of the two C5a receptors: C5aR (D88) and C5L2 [79,80]. The vast majority of these agents are evaluated in trials for diseases not concerning the kidney as psoriasis, rheumatoid arthritis, the Alzheimer disease, and colitis [77].

ADC-1004 is a promising molecule that is a selective antagonist of the C5aR for the treatment of IRI. The drug hits a target that is accessible prior to reperfusion and is still in preclinical phase [77].

The only anti C5aR molecule under investigation for renal disease is CCX168, which is not really a biotherapy, but a small molecule targeting the C5aR. As the complement activation is crucial for the development of ANCA associated renal vasculitis and C5a receptor mediates neutrophil activation, this drug is being tested in human disease (NCT 01363388) [76]. In animal models CCX168 significantly improved the glomerular lesions, reducing both hematuria and proteinuria [81,82].

C3 inhibition

In theory, the blockade at the level of C3 should be more effective than the anti C5 therapy, in particular for the C3 glomerulopathies where the C3 convertase activation is prevalent over the C5 convertase. Soluble CR1 **(sCR1)** is a protein that regulates the C3 convertase. CR1 is a cell surface glycoprotein expressed on several cells among which monocytes, APCs, T and B cells and podocytes. As a consequence sCR1 may modulate the complement cascade on all these cells that express on their surface CR1 [83-85].

Recently, Zhang et al from Iowa University [86] reported the beneficial effects of a recombinant sCR1 (CDX-1135) in mice deficient in factor H. This group is currently enrolling for a small phase I trial patients affected by DDD (NCT01791686) [87]. The beneficial effects of another sCR1 (Mirocept, APT070) have been widely described by Sacks [88] and is currently the subject of a

large scale study in kidney transplantation to test the superiority of Mirocept in the prevention of IRI in cadaveric renal allografts [89].

TT30 is another promising biologic molecule. TT30 is a novel therapeutic fusion protein combining the C3 binding domain of complement receptor 2 with the inhibitory region of factor H [90]. This biologic agent is efficient in different animal models and is actually in a phase I safety study.

C1 inhibitors

Purified or recombinant C1 inhibitor **(CI-INH)** is a host serine protease inhibitor that is able to block the complement cascade. The first clinical indication of C1-INH has been the hereditary angioedema. To date 3 clinical trials are ongoing in renal transplantation. The first two clinical trials (NCT01134510, NCT01147302) had the aim of preventing or treating the acute ABMR, and the study results document the efficacy of the drug. The third study (NCT02134314) [91] has the aim of preventing DGF in transplant patients receiving deceased donor kidneys. In addition, Curci et al documented the effectiveness of C1-INH in inhibiting the Akt pathway involved in the Endothelial-Mesenchimal Transition **(EndMT)** [20].

Targeting B cells and antibody network

B cell depletion

Rituximab is a monoclonal antibody targeting the CD20 receptor on the B cell surface: thus obtaining a peripheral B cell depletion. Rituximab is probably one of the most widely used biological agents both for patients with immune-mediated glomerulonephritis and for renal transplant patients.

Among the immune-mediated GN the most frequent conditions in which rituximab is used are:

ANCA vasculitis [92,93]

The rationale for the use of rituximab in ANCA-Associated Vasculitis **(AAV)** is very high: indeed the B cell activation occurs in AAV and ANCA are produced by the B cells and autoreactive B cells are present in granulomatous lesions [94,95].

ANCA high rate mortality has been reduced in the last years with therapies based on cyclophoshamide and glucocorticoids high dose. Moreover, several clinical and therapeutical aspects still remain to be answered. Among these, the treatment related toxicity, the remission induction and how to treat the refractory and the relapsing disease.

Two randomized trials have compared rituximab to cyclophosphamide for the remission induction in severe AAV [96,97]. These two trials (RAVE, RITUXVAS) had some differences in inclusion/exclusion criteria, but overall both trials reported similar remission rate for the cyclophosphamide and the rituximab groups. In addition, in the RAVE trial, rituximab exhibited a higher efficacy in patients with relapsing disease. A peculiar condition is that concerning the

patients' dialysis dependent. An ongoing PEXIVAS plasma exchange trial (NCT00987389) [98] is enrolling 500 patients including those dialysis dependent to document the rituximab efficacy.

For relapsing AAV, the RITAZAREM trial compares rituximab to azathioprine, after rituximab induction therapy (NCT01697267) [99]. A different strategy has been examined in the MAINRITSAN trial, where rituximab maintenance therapy is administered after cyclophosphamide reduction. The results of the study have been recently published [100]. Finally, a further trial has been proposed to compare two rituximab 500 mg dosing strategies: either with fix dosing every six months or with dosing according on the B cell and ANCA return (NCT01731561) [101].

Membrano-proliferative glomerulonephritis (MPGN)

A study from Saadoun et al [27] documented the rituximab superiority respect to the standard therapy when rituximab is added to PEG-IFN alpha/ribavirin in treating HCV-mixed cryoglobulinemia.

A clinical trial sponsored by the Mayo clinic is ongoing (NCT00275613) [102] to treat the MPGN with DD, but the study results are not yet known.

Membranous nephropathy

As aforementioned circulating antibodies are strongly involved in the pathogenesis of MN and are directed against neutral endopeptidase [21] as well as against other podocyte enzymes as M-type phospholipase-2-receptor [22], aldose reductase and manganese superoxide dismutase [23-25]. Evidence that B cells play a crucial role in the pathogenesis of the disease as auto-antibody-producing cells, provided the background for explorative studies. After the initial successful treatment of 8 patients [103], other groups have reported the rituximab efficacy in MN [104-106]. By 2012, a single-centre cohort study found a remission of the NS in 65% of 100 patients and the treatment effect was time-dependent [107]. Recent data documenting that an anti-PLA2R antibody titer reduction preceded Nephritic Syndrome **(NS)** remission, confirmed that the inhibition of B cell antibody production, caused the clinical remission [108].

To date 6 Clinical trials are ongoing on the use of rituximab in MN and overall 548 patients have been enrolled [109] (Table 3).

Table 3: Rituximab for membranous nephropathy.

Rank	Identifier	Status	Patients enrolled	Study name
1	NCT01508468	Active	80	Evaluate Rituximab Treatment for Idiopathic Membranous Nephropathy
2	NCT01955187	Recruiting	148	Sequential Therapy with Tacrolimus and Rituximab in Primary Membranous Nephropathy
3	NCT01180036	Recruiting	126	MEmbranous Nephropathy Trial Of Rituximab **(MENTOR)**
4	NCT00405340	Completed	20	Rituximab in the Treatment of Idiopathic Membranous Nephropathy
5	NCT00977977	Recruiting	30	Rituximab plus Cyclosporine in Idiopathic Membranous Nephropathy
6	NCT00425217	Complated	15	Rituximab in Membranous Nephropathy

Several biologics are used for the treatment of LN with different results (Table 4).

Table 4: Biologics in LES.

Target	Drug name	Trial phase	Trial status	Duration, months	Nephritis class	NCT number
CD20	rituximab	2	completed	12	III, IV, V	NCT00556192
	rituximab	3	completed	12	III, IV	NCT00282347
	rituximab	3	recruiting	24	III, IV, V	NCT01673295
	rituximab	3	recruiting	12	III, IV, V	NCT01773616
	ocrelizumab	3	ongoing	12	III, IV	NCT00626197
CD22	epratuzumab	1	completed	1	Active lupus nephritis	NCT00011908
CD74	milatuzumab	2	recruiting	24	Not specified	NCT01845740
BLys/BAFF	belimumab	3	recruiting	24	Active lupus nephritis	NCT01639339
CTLA4	abatacept	1	completed	2	SLE	NCT00705367
	abatacept	1/2A	completed	3	III, IV, V	NCT00094380
	abatacept	2	ongoing	12	SLE	NCT00774852
	abatacept	3	ongoing	12	III, IV	NCT01714817
CD40L	Bg9588	2	completed	5	III, IV	NCT00001789
IL-6	CNTO136	2	completed	6	III, IV	NCT01273389
	MRA	1	completed	3	Moderately active lupus	NCT00046774
IFN- γ	AMG811	1	recruiting	6	III, IV	NCT00818948

BLys= B Lymphocyte stimulator; **BAFF**= B cell activating factor; **CTLA4**= Cytotoxic T-Lymphocyte Antigen 4; **TWEAK**= TNF-like weak inducer of apoptosis; **IL-6**= Interleukin 6; **IFN**-γ= Interferon gamma

The B cells and the Short-Lived Plasma Cells in patients with LN provide a rationale for the use of drugs, as rituximab, that deplete CD20 positive B cells and short lived plasma cells [36].

The first trial with rituximab in LN was unsuccessful probably because the trial design was an add-on to standard of care with MMF and steroids. As a consequence, the LUNAR trial failed to meet its primary endpoint of 20% superiority [110]. However a revision of the trial at 78 weeks of follow-up, strongly suggested that rituximab had a beneficial effect [111]. To date an alternative way to use rituximab (i.e, without steroids) is ongoing [112] in a large multicenter trial under the name of RITUXILUP TRIAL.

RING, another ongoing trial led by Houssiau et al (NCT01673295) [113] is aiming to evaluate rituximab in the patients that failed to achieve complete remission with the standard of care treatment. To date, 4 clinical trials with rituximab are ongoing in LN [114] (Table 5).

Table 5: Randomized clinical trials with Rituximab in Lupus Nephritis.

Rank	Identifier	Status	Patients enrolled	Study name
1	NCT01673295	recruiting	194	RING RItuximab for lupus Nephritis with remission as a Goal
2	NCT02260934	recruiting	40	Rituximab and Belimumab for Lupus Nephritis
3	NCT00282347	completed	144	A Study to Evaluate the Efficacy and Safety of Rituximab in Subjects with International Society of Nephrology/Renal Pathology Society **(ISN/RPS)** 2003 Class III or IV Lupus Nephritis
4	NCT01773616	recruiting	252	Trial of Rituximab and Mycophenolate Mofetil Without Oral Steroids for Lupus Nephritis

The usefulness of rituximab has been documented also in patients with anti-glomerular basement membrane disease and fibrillary glomerulonephritis [29,115]. Surprisingly, only one study is ongoing for IgA-GN. Moreover, the study is small and is enrolling only 54 patients (NCT00498368) [116].

The use of rituximab was documented to be useful also in diseases with no recognized nephrotoxic auto antibodies, such as the NS in the course of minimal change disease (MCD) and FSGS. The studies concerning these diseases are small, without well established enrolling criteria, often retrospective and without a clear-cut distinction between MCD and FSGS. All these studies have been recently reviewed in two papers by Kronbinchler et al [117,118]. According these studies, rituximab is effective in reducing the number of relapses in frequently relapsing and steroid-dependent NS due to MCD and FSGS, even if these findings should be confirmed by controlled, prospective studies. To date, only four controlled studies are ongoing in phase II/III, but enrolling overall 114 patients [119].

Rituximab has been used in renal transplantation in several circumstances. Firstly has been used as desensitization therapy, alone or in combination with other drugs. Rituximab allowed a decrease of the circulating antibodies precluding transplantation between two subjects. Later on rituximab has been used as treatment of steroid resistant humoral rejection [120].

The use of rituximab as desensitization therapy has been extensively reviewed by Sir Peter Morris, President of the Centre for Evidence in Transplantation [121]. Though several clinical trials have been made, a lack of randomized evidence precluded a meta-analysis and only a narrative review has been conducted.

The studies may be divided as follows:

Rituximab for desensitization in AB0 incompatible recipients.

Rituximab for de-sensitization in recipients with a positive complement-dependent citotoxicity cross-match.

Rituximab for desensitization in recipients with positive DSAs.

For every group considered, an evidence of limited quality was identified to support the use of Rituximab desensitization in highly sensitized recipients. This fact highlights the need for high quality RCTs to better define the role of rituximab in addition to standard desensitization protocols.

The rational to treat humoral rejection antibody related with an anti CD20 molecule is strong. However, in a recent systematic review [122], the author concluded that only small, nonrandomized controlled studies suggested some benefit for drugs as rituximab or bortezomib and that larger RCTs are still required.

To date 1 RCT is ongoing to test the efficacy of rituximab on humoral acute rejection (NCT01117662), 2 RCTs are ongoing for chronic humoral rejection (NCT00476164, NCT00568477) [123].

More recently, other anti-CD20 antibodies have been developed with increased activity and reduced immunogenicity than rituximab.

Humanized ocrelizumab has been used in a RCT (BELONG, NCT00626197) [124] for the treatment of LN, but the study documented a high incidence of infections [125]. No study in renal transplantation is ongoing with ocrelizumab.

Similarly, the fully humanized ofatumumab is not yet used neither in renal diseases nor in transplantation.

Another depleting agent widely used in transplantation is the alemtuzumab (CAMPATH-1H). Alemtuzumab is an anti-CD52 antibody targeting not only the B cells but also the T cells and the monocytes. Its use in nephrology is still limited to one RCT for relapsing ANCA vasculitis (NCT01405807) [126]. The results of the study are still unknown.

The use of alemtuzumab in renal transplantation is principally used in the induction therapy and in the treatment of refractory rejection (Table 6). More than 30 RCTs [127] have validated the use of alemtuzumab in the induction therapy. Recently a Collaborative Group in a RCT (NCT01120028) [128] documented the higher efficacy of alemtuzumab induction in comparison to basiliximab induction. The same trial as well as other studies documented the feasibility of reducing or withdrawing the CNI as well as the steroids. Clearly, the benefit of such strategy is the potential absence of chronic nephropathy. The substitution with mTOR inhibitors seems less safe [129]. However, other studies do not agree with the efficacy of the alemtuzumab induction therapy. Indeed, Noureldeen et al [130] found a higher incidence of ABMR in patients who received alemtuzumab induction than those who received ATG induction. The use of alemtuzumab to treat refractory acute rejection is still limited and, according some study, does not have high efficacy, principally when given as single dose [131].

Table 6: Randomized Controlled Trials with alemtuzumab in renal transplantation.

Rank	Identifier	Status	Patients enrolled	Study name
1	NCT00183248	completed	9	Using Donor Stem Cells and Alemtuzumab to Prevent Organ Rejection in Kidney Transplant Patients
2	NCT00078559	completed	10	Combination Immunosuppressive Therapy to Prevent Kidney Transplant Rejection in Adults
3	NCT00113269	completed	501	Safety/Efficacy of Induction Agents With Tacrolimus, MMF, and Rapid Steroid Withdrawal in Renal Transplant Recipients
4	NCT00166712	active	40	A Trial of Two Steroid-Free Approaches Toward Mycophenolate Mofetil-Based Monotherapy Immunosuppression
5	NCT01213329	terminated	52	Immunophenotyping of Peripheral T Cells After T Cell Depletion With Alemtuzumab
6	NCT00685061	completed	90	Thymoglobulin Versus Campath-1H Versus Daclizumab in Adult, Primary Deceased Donor Renal Transplantation
7	NCT00214266	completed	31	A Pilot Study of Campath-1H Induction Therapy Combined With CellCept® Therapy to Allow for a Calcineurin Inhibitor Free Regimen After Renal Transplantation
8	NCT00147381	completed	197	Effectiveness and Safety of Campath in Combination With Tacrolimus Monotherapy to Prevent Kidney Graft Rejection
9	NCT00309270	completed	21	Low Dose Sirolimus or CsA-Based Maintenance Immunosuppression After Induction With Campath-1 in Kidney Transplantation
10	NCT01729494	recruiting	315	Belatacept Early Steroid Withdrawal Trial
11	NCT00681343	completed	38	Thymoglobulin Versus Campath-1H Versus Daclizumab in Adult, Primary Living Donor Renal Transplantation
12	NCT00316810	completed	30	Simultaneous Pancreas-kidney Transplantation With Campath Protocol
13	NCT01046955	completed	38	Thymoglobulin Versus Alemtuzumab Versus Daclizumab in Living Donor Renal Transplantation
14	NCT01120028	active	800	Campath, Calcineurin Inhibitor Reduction and Chronic Allograft Nephropathy
15	NCT00214201	completed	40	Campath-1H Induction to Allow Discontinuation of Calcineurin Inhibitors After Renal Transplantation
16	NCT00365846	completed	29	"A Pilot Study to Determine the Safety of Campath-1H (Anti-CD52) Therapy in Primary Renal Allograft Transplantation"
17	NCT00001984	completed	5	Effectiveness of the Investigational Drug Campath-1H in Preventing Rejection of Transplanted Kidneys
18	NCT01935128	completed	50	Evaluation of Calcineurin-inhibitor Reduction With Conversion at 3 Months to Everolimus/Reduced Tacrolimus in Renal Transplant Recipients Following Campath® Induction
19	NCT01172418	completed	200	Randomized Trial of 2 Antibody Induction Steroid Avoidance Protocols

Milatuzumab is another depleting agent targeting CD74 that is expressed on both T and B lymphocytes. To date is tested for SLE and LN (NCT01845740) [132], but no result has been yet given. No trial is ongoing in renal transplantation.

Bortezomib also merits a consideration in the chapter of B depleting agents. Bortezomib is an N protected dipeptide, a relatively small molecule, therefore is not a biologic drug, even if some author erroneously categorizes Bortezomib as a biologic drug. Bortezomib has been the first drug approved as a proteosome inhibitor in the field of the myeloma treatment. The main mechanism of Bortezomib is to inhibit the degradation of inhibitor kB molecule, therefore preventing the NFkB mediated cell activation. As a consequence, an inhibition of degradation of cell cycle regulatory proteins happens causing the cell cycle arrest and the apoptosis [120].

In nephrology only one pilot study in IgA nephropathy is ongoing (NCT01103778) [133]. Another study attempting to use Bortezomib in LN has been withdrawn (NCT01169857) [134].

In transplantation, Bortezomib is used in desensitization to decrease the level of preformed DSAs or in the treatment of acute or chronic ABMR.

In desensitization, Everly et al [135] was able to obtain a significant reduction in DSAs with an improved long-term allograft function. To date, 6 RCTs are ongoing to test Bortezomib in a desensitization strategy (136). Similarly, to date two RCTs are testing Bortezomib in the treatment of chronic or acute ABMR (NCT02201576, NCT01873157) [137].

Blocking B cell activation

Belimumab is a monoclonal antibody that inhibits the B-cell-Activating Factor **(BAFF)**. This agent has been approved for the treatment of SLE. The studies that led to the approval for SLE (BLISS-56 and BLISS-76) [138] excluded patients with severe LN, but new data and a retrospective analysis suggested a beneficial effect also upon LN [139]. To date, two RCTs are ongoing to evaluate the efficacy of Belimumab on LN (NCT1639339, NCT02260934) [140]. Belimumab is now being evaluated also for membranous nephropathy (NCT01610492) [141] and for ANCA vasculitis (BREVAS study, NCT01663623) [142].

Since 2011, the use of Belimumab in renal transplantation has been speculated [143]. One RCT is now ongoing to evaluate belimumab in the desensitization strategy and in the prevention of rejection (NCT01536379) [144].

Two other newest agents anti BAFF, tabalumab and blisibimod are now being tested for glomerular diseases. The first for LN (NCT01196091, NCT01488708) [145]. The trials are still ongoing. The RCTs to use blisibimod for LN and IgA GN (NCT02074020, Brilliant Study NCT02052219 failed to document the drug efficacy [146].

Atacicept is a transmembrane activator and a calcium modulator and cyclophilin ligand interactor-immunoglobulin fusion protein that inhibits B cell stimulation by blocking both BLyS and APRIL ligands [147]. It has been evaluated in two RCTs for LN, but both studies were stopped because of the high number of infections [148]. To date Atacicept is not on trials for renal transplantation.

Epratuzumab is a monoclonal antibody targeting CD22 on mature B cell. The drug induces mild B cell depletion, but marked B cell anergy. It improves moderate-to-severe non renal flares in SLE patients, but efficacy data on lupus nephritis are not yet available [149].

Inhibiting antibody network

The administration of high dose Intravenous Human Immunoglobulins **(IVIG)** has the ability to regulate cellular immunity including the innate and the adaptive components. In particular, IVIG interfere with the antibody network in several ways: regulating B cell repertoire, neutralizing preformed antibodies, blocking anti-idiotype of alloantibodies, inducing B cell apoptosis, inhibiting dendritic cell maturation and macrophages [150]. IVIG have been used in nephrology for ANCA disease [151], for IgA nephropathy [152] and for membranous nephropathy [153]. Recently its use in nephrology became less frequent and, to our knowledge, to date only one RCT has been conducted for idiopathic thrombocytopenic purpura (NCT00699140) [154]. However

the early study termination and the small number of patients enrolled did not allow to draw any conclusion.

In renal transplantation IVIG are principally used in desensitization therapy and in the treatment of chronic humoral rejection.

The most common protocol used in adult patients in the USA was based on a combination of IVIG and Plasmapheresis **(PF)** and preoperative rituximab [155]. The combination of IVIG and rituximab was used by the Jordan group to reduce the titer of preformed anti- HLA antibodies in highly sensitized patients awaiting renal transplantation [156]. To date 8 RCTs are ongoing [157] to further evaluate the efficacy of IVIG in the desensitization therapy. Almost always, IVIG are given in association with other depleting agents (Table **7**). IVIG with rituximab are also used in patients with chronic ABMR. Small case series documented the efficacy of this association therapy for chronic ABMR [158,159], but to date no RCT is ongoing.

Table 7: Intravenous immunoglobulins for desensitization in Renal Transplantation.

Rank	Identifier	Status	Patients enrolled	Study name
1	NCT00642655	completed	20	Rituximab and Intravenous Immunoglobulin (IVIG) for Desensitization in Renal Transplantation
2	NCT00986947	completed	27	Desensitization of Highly Sensitized Deceased Donor Renal Transplantation Candidates
3	NCT02115503	recruiting	162	A Prospective, Global, Multi-center, Treatment Registry Study of Intravenous Immunoglobulin Maintenance Therapy in Alloantibody Positive Renal Allograft Recipients
4	NCT01502267	Enrolling by invitation	2	Desensitization Protocol for Highly Sensitized Patients on the Waiting List for Kidney Transplant
5	NCT00000935	completed	100	An Evaluation of IV Gamma Globuklin As a Method to Improve Kidney Transplant Survival in Patients with End-Stage Renal Disease who are Highly Sensitized to Transplant Antigens
6	NCT01178216	recruiting	75	Use of Immune Globulin (IVIG) plus Rituximab for Desensitization in Highly HLA Sensitized Patients Awaiting Deceased Donor Kidney Transplantation
7	NCT00176059	completed	50	Immunoregulatory Effects of Immunoglobulin Induction Therapy in Renal Transplant Reciients

Targeting T cells and T-cell Activation

Biologic agents targeting T cells and inhibiting T-cell activation are principally used in renal transplantation. Only recently, some biologic, principally acting on co-stimulation pathway, is used in RCTs for glomerular diseases.

Non depleting agents

The most common non depleting agents are basiliximab and daclizumab. Both these drugs are monoclonal antibodies anti CD25 receptor, inhibiting T-cell activation induced by the Interleukin-1 **(IL-1)**. In renal transplantation these drugs are used in the induction therapy. Comprehensive information on the efficacy and the safety of anti CD25 inhibitors derives from a Cochrane

database large systematic review involving 71 adult and pediatric trials with 10520 patients. The review documented a decreased risk of acute rejection in the first year after transplantation by 25% and a reduction of 1-year graft loss by 25% [160]. However, two pediatric RCTs proved that the addition of antiCD 25 Ab to triple maintenance therapy is not justified, as the incidence of the rejection or the patient and graft survival were not different with and without induction [161,162]. Anti CD 25 mAb induction has been also used to attempt steroid minimization. A monoclonal induction with anti CD25 mAb with combination of TAC/MMF therapy allowed an early steroid withdrawal [163]. To date an ongoing multicenter study aims at verifying the efficacy of giving mAb anti CD25 with everolimus, with reduced exposure to TAC (CRADLE, NCT01544491) [164]. Anti CD25 agents are not used to date in nephrology.

Depleting agents

Alemtuzumab has been already described discussing the B cell depleting agents. The antithymoglobulin are the most common depleting agent targeting T cells. Among the different types of ATG, the most commonly used are the rabbit ATG, which are better tolerated and more efficient for both the prevention and the treatment of rejection [165, 166]. The rATG blocks several receptors, causing cell dysfunction, lysis and long-lasting depletion. Two short-term randomized trials of deceased donor recipients documented in the past a reduced rejection rate using rATG in the induction therapy [167,168].On the other hand, rATG use caused reversible leucopenia, thrombocytopenia and infections. A recent meta-analysis of 6 randomized studies including 853 patients showed no differences between ATG and basiliximab for the outcomes including Biopsy Proven Acute Rejection **(BPAR)**, DGF, graft loss and patient death [169]. In contrast, results of a larger trial using moderate to high risk deceased donor recipients, documented an improved composite endpoint that favored rATG [170].

Alefacept is another depleting agent. Alefacept is a CD-directed LFA-3Fc fusion protein that consists of the exteracellular CD2 binding portion of the human Leukocyte Function Antigen 3 **(LFA-3)** linked to the Fc portion of human IgG1 [171]. The drug, indicated for the treatment of moderate to severe chronic plaque psoriasis was voluntary withdrawn from the market by Astellas by 2011 [172]. Prior to discontinuation, alefacept has been used in a phase II de novo study of adult kidney transplant patients with good results, but an higher incidence of malignancies [173].

Inhibiting T-cell activation and blocking co-stimulation

Efalizumab works as immunosuppressant by binding to the CD11a subunit of lymphocyte function associated antigen 1 (LFA-1) and by inhibiting lymphocyte activation and cell migration out of blood vessels into tissues. The drug was indicated for treatment of chronic-to moderate-to severe plaque psoriasis, but has been associated to increased risk for progressive multifocal leukoencephalopathy and was withdrawn from the market by 2009 [174]. Likewise, clinical trials in renal transplant recipients have not been successful due to higher rates of lymphoproliferative diseases [175].

Another strategy is to block the co-stimulation pathways.

The block of CD40-CD154 interaction has been attempted by several humanized anti CD154 mAbs and showed efficacy in non-human primate [176]. Trials in man failed because of thromboembolic events [177]. It was assumed that blocking CD40-CD154 pathway via CD40 rather than CD154 might allow an immunosuppressive effect avoiding thromboembolic events. In a recent study a fully human anti CD40 mAb (ASKP1240) was evaluated with good results in cynomolgus monkeys [178]. Two RCTs in phase II are to date ongoing to test ASKP1240 in renal transplantation in humans (NCT01780844, NCT01279538) [179].

Biologic drugs blocking the co-stimulation pathway between CD80 on APCs and CD28 on T cells are abatacept and belatacept. These drugs are used in nephrology and in renal transplantation as well.

Abatacept and belatacept are both CTLA-4-Ig fusion proteins that bind to both CD80 and CD86 on the surface of APCs, thereby blocking both CD28 co-stimulatory signals as well as CTLA-4 co-stimulatory signals. Belatacept has enhanced activity thanks to two amino-acids substitution [180].

Abatacept is principally used in glomerular diseases, LN in particular, while belatacept is to date widely used in 40 RCTs in renal transplant patients. According to a recently published study abatacept allows the reduction of proteinuria in nephritic SLE patients, but does not improve the overall complete response rate [181]. Similarly, the results of the ACCESS trial (NCT00774852) [182], revealed that the addition of abatacept on top of a cyclophoshamide-based induction therapy does not improve the remission rate of proliferative LN. Overall, abatacept failed to succeed to reach the primary endpoint in the randomized trial on the induction phase of LN classes III and IV, although abatacept therapy had some effects on plasma levels of dsDNA autoantibodies and on complement normalization [181]. Three other RCTs are to date ongoing to evaluate the effect of abatacept on LN (NCT00705367, NCT00094380, NCT01714817) [183]. Moreover, a further phase I/II trial evaluated the efficacy of abatacept in mild relapsing Wegener's granulomatosis (NCT00468208) [184]. In addition, recently Yu et al [185] reported the usefulness of abatacept in 5 patients with FSGS with proteinuric disease.

Belatacept is the first immunosuppressant that demonstrated a real benefit over a calcineurin inhibitor based regimen [186,187].

In a recent paper, Masson et al. reviewed five studies that compared belatacept and CNI, reporting data from a total of 1535 kidney transplant recipients [188]. The conclusions were that there is no difference in the effectiveness of belatacept and CNI in preventing acute rejection, graft loss and death, but the treatment with belatacept is associated with less chronic kidney scarring and better kidney transplant function. In addition, treatment with belatacept is associated with better blood pressure and lipid profile. The authors conclude that long-term, fully reported and published studies comparing belatacept versus tacrolimus are needed.

To date several RCTs are ongoing to evaluate the efficacy of belatacept in different clinical conditions. Two trials are evaluating the belatacept efficacy in patients with DGF (NCT01837043, NCT02134288) [189], one RCT is evaluating the feasibility of steroid withdraw (NCT00402168) [190], one RCT the use of belatacept in pediatric patients (NCT01791491) [191].

Blocking Systemic Inflammation

These biologics should be considered as the new frontier of immunosuppression. To date their use in RCTs is principally in the field of renal diseases. Their involvement is also known in the field of transplantation, but in this case their use is just at the beginning, with the exception of islet transplantation.

Although drugs targeting molecules involved in systemic inflammation as TNF alpha, IL-1 or IL-6 are not used in primary glomerulonephritis, their use seems to be beneficial on renal function when used in the case of systemic diseases as amyloidosis or inflammatory systemic diseases [192].

Two phase I/II studies for the treatment of FSGS with adalimumab (a monoclonal antibody anti TNF alpha) failed to document the efficacy of the drug with respect to standard therapy (NCT00814255; NCT00193648) [193]. Infliximab, a monoclonal Ab against TNF alpha was effective in the treatment of Wegener granulomatosis [42]. More recently the drug was able to improve severe lupus nephritis [194]. To date one RCT has been completed to the use of infliximab in renal vasculitis (NCT00753103), but the results are not yet known [195].

Etanercept is a fusion protein between IgFc and the extracellular domain of p75 receptor to TNF alpha. Even if a RCT to evaluate etarnecept in ANCA vasculitis showed no beneficial effect [43], to date one RCT has provided beneficial results for the treatment of lupus nephritis (NCT00447265) [196].

Other biologics targeting tissue inflammation and studied in RCTs for lupus nephritis are mAbs against IL-6 (tocilizumab and sirukimab or CNTO 136), and against IL-12 (ustekinumab) (NCT00144573; NCT01273389; NCT02349061) [197]. The study results are to date not known.

Recently, a newer cytokine called TNF-like weak inducer of apoptosis (TWEAK) has been documented to have a pivotal role in the physiopathology of lupus nephritis. This cytokine is generated by inflammatory cells as leukocytes or macrophages that infiltrate the kidney. In animal models the inhibition of TWEAK caused an improvement of renal injury [44]. BIIB023 is a mAb against TWEAK. Unfortunately the ATLAS study (Anti-TWEAK in Lupus Nephritis Patient Study) (NCT01499355) [198] was not able to document the efficacy of the drug and the RCT was terminated.

IFN alpha and IFN gamma are other cytokines targeted principally in LN. Rontalizumab is a monoclonal antibody targeting IFN alpha. After a RCT (NCT00962832), the drug efficacy has been

recently published [199]. Other drugs targeting IFN alpha are sifalimumab [200] and AGS-009 [201]. Both drugs are to date un phase I study. AMG-811 targets IFN gamma and a RCT phase for LN has been completed, but the results not yet known (NCT00818948) [202].

Immunization is a different strategy. IFN alpha kinoid is an anti IFN alpha therapeutic vaccine for the treatment of SLE. Neovacs has shown to neutralize all the 13 subtypes of IFN alpha in the serum of lupus patients [203]. A RCT is now ongoing with IFN alpha kinoid (NCT01058343) [204]. Finally another biologic used in RCT for SLE is a mAb directed against type I IFN receptor (MEDI-546, NCT01438489) [205].

A recent safety study was conducted with Anti-Migration Inhibitory Factor **(MIF)** antibody (NCT01541670) [206].

A fusion protein is OPL-CCL2-LPM. This fusion protein binds to macrophages and is a promising target to decrease macrophage-dependent inflammation. This molecule has been shown to be effective in an animal model of mesangioproliferative GN and has been evaluated in a safety study for IgA nephropathy (NCT00856674) [207]. The study was terminated without results in man.

In addition, preclinical experiments suggest that adding CCL2 inhibitor to a low dose of cyclophosphamide is as efficient as high dose cyclophosphamide, but avoids the side effects as myelosuppression and lymphocyte ablation [208]. A first trial documented a positive effect on proteinuria [209].

The basis for a relevant physiopathological role of mediators of inflammation in kidney transplantation are strong, nevertheless, the RCTs attempting to inhibit inflammation mediators in transplantation are relatively few in comparison to glomerulonephritis.

Intragraft inflammatory cascades are initiated with donor's brain death and followed by IRI; realyzing a cascade of proinflammatory cytokines, chemokines and an up-regulation of adhesion molecules [210,211].

IL-6 is a key inflammatory cytokine induced by IRI as documented by several authors [212,213]. Indeed renal transplant recipients display high serum and urinary levels of IL-6 immediately post transplantation and during AR [214,215].

TNF alpha is another proinflammatory cytokine involved in IRI and its targeting reduced expression of TNF alpha and reduced IRI [216,217].

Targeting adhesion molecules represents another promising approach to reduce leukocyte infiltration [218].

The fusion protein against TNF alpha, etanercept is the most widely studied agent for islet transplantation, among the aforementioned inhibitors of the proinflammatory molecules. The anti-inflammatory agents have been incorporated in immunosuppressive regimens in recent clinical allogenic islet transplant protocols [219,220]. A recent review has summarized progress

related to this approach [221]. To date 3 RCTs are using etanercept in islet transplantation (NCT02464878; NCT02713997; NCT00468117) [222]. Recently Anakinra, a mAb anti IL-1R has been added to etarnecept for islet transplantation [223]. One RCT has been completed documenting the possibility of a calcineurin free immunosuppression with the use of anakinra (NCT01346085) [224].

Tocilizumab is a mAb against IL-6R and is to date tested in two RCTs in kidney transplantation aiming to reduce the inflammation in transplant patients either highly sensitized (NCT01594424) [225] or not sensitized patients (NCT02108600) [226].

Proinflammatory cytokines are also involved in determining chronic damage after transplantation and renal fibrosis. CCL2 [Chemokine (C-C ligand) motif ligand 2] is a CCR2 receptor chemokine attracting macrophages, T cells and NK cells. This molecule is involved in determining IF/TA as documented by Ho et al [227].

TGF beta is also involved in the pathogenesis of chronic rejection in kidney transplant [228]. Guan et al. [229] have evaluated the efficacy of anti TGF beta mAb in the prevention of chronic rejection. They documented the reduction of the severity of chronic rejection in a rat model.

Also the Bone Morphogenic Protein **(BMP-7)** antagonizes TGF beta and has powerful renoprotective and anti fibrotic effect [230,231]. The administration of BMP-7 reduces glomerular and tubulointerstitial fibrosis in different clinical conditions among which the kidney transplantation.

References

1. Ponticelli C, Coppo R, Salvadori M. Glomerular diseases and transplantation: similarities in pathogenetic mechanisms and treatment options. Nephrol Dial Transplant. 2011; 26: 35-41.
2. Mogensen TH. Pathogen recognition and inflammatory signaling in innate immune defenses. Clin Microbiol Rev. 2009; 22: 240-273.
3. Anders HJ, Schlondorff DO. Innate immune receptors and autophagy: implications for autoimmune kidney injury. Kidney Int. 2010; 78: 29-37.
4. Rasmussen SB, Reinert LS, Paludan SR. Innate recognition of intracellular pathogens: detection and activation of the first line of defense. APMIS. 2009; 117: 323-337.
5. Suzuki Y, Tomino Y. The mucosa-bone-marrow axis in IgA nephropathy.
6. Suzuki H, Suzuki Y, Narita I, Aizawa M, Kihara M. Toll-like receptor 9 affects severity of IgA nephropathy. J Am Soc Nephrol. 2008; 19: 2384-2395.
7. Coppo R, Camilla R, Amore A, Peruzzi L, Daprà V. Toll-like receptor 4 expression is increased in circulating mononuclear cells of patients with immunoglobulin A nephropathy. Clin Exp Immunol. 2010; 159: 73-81.
8. Fujinaka H, Nameta M, Kovalenko P, Matsuki A, Kato N. Periglomerular accumulation of dendritic cells in rat crescentic glomerulonephritis. J Nephrol. 2007; 20: 357-363.
9. Saiga K, Tokunaka K, Ichimura E, Toyoda E, Abe F. NK026680, a novel suppressant of dendritic cell function, prevents the development of rapidly progressive glomerulonephritis and perinuclear antineutrophil cytoplasmic antibody in SCG/Kj mice. Arthritis Rheum. 2006; 54: 3707-3715.
10. Fiore N, Castellano G, Blasi A, Capobianco C, Loverre A. Immature myeloid and plasmacytoid dendritic cells infiltrate renal tubulointerstitium in patients with lupus nephritis. Mol Immunol. 2008; 45: 259-265.
11. Tucci M, Calvani N, Richards HB, Quatraro C, Silvestris F. The interplay of chemokines and dendritic cells in the pathogenesis of lupus nephritis. Ann N Y Acad Sci. 2005; 1051: 421-432.

12. Barbour TD, Pickering MC, Cook HT. Recent insights into C3 glomerulopathy. Nephrol Dial Transplant. 2013; 28: 1685-1693.

13. Roumenina LT, Loirat C, Dragon-Durey MA, Halbwachs-Mecarelli L, Sautes-Fridman C. Alternative complement pathway assessment in patients with atypical HUS. J Immunol Methods. 2011; 365: 8-26.

14. Allam R, Anders HJ. The role of innate immunity in autoimmune tissue injury. Curr Opin Rheumatol. 2008; 20: 538-544.

15. Chen M, Daha MR, Kallenberg CG. The complement system in systemic autoimmune disease. J Autoimmun. 2010; 34: J276-286.

16. Land W. Innate alloimmunity: history and current knowledge. Exp Clin Transplant. 2007; 5: 575-584.

17. Castellano G, Melchiorre R, Loverre A, Ditonno P, Montinaro V. Therapeutic targeting of classical and lectin pathways of complement protects from ischemia-reperfusion-induced renal damage. Am J Pathol. 2010; 176: 1648-1659.

18. Fuquay R, Renner B, Kulik L, McCullough JW, Amura C. Renal ischemia-reperfusion injury amplifies the humoral immune response. J Am Soc Nephrol. 2013; 24: 1063-1072.

19. Pratt JR, Basheer SA, Sacks SH. Local synthesis of complement component C3 regulates acute renal transplant rejection. Nat Med. 2002; 8: 582-587.

20. Curci C, Castellano G, Stasi A, Divella C, Loverre A. Endothelial-to-mesenchymal transition and renal fibrosis in ischaemia/reperfusion injury are mediated by complement anaphylatoxins and Akt pathway. Nephrol Dial Transplant. 2014; 29: 799-808.

21. Debiec H, Guigonis V, Mougenot B, Haymann JP, Bensman A, et al. Antenatal membranous glomerulonephritis with vascular injury induced by anti-neutral endopeptidase antibodies: toward new concepts in the pathogenesis of glomerular diseases. J Am Soc Nephrol. 2003; S27-S32.

22. Ronco P, Debiec H. Anti-phospholipase A2 receptor antibodies and the pathogenesis of membranous nephropathy. Nephron Clin Pract. 2014; 128: 232-237.

23. Beck LH, Bonegio RG, Lambeau G, Beck DM, Powell DW. M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. N Engl J Med. 2009; 361: 11-21.

24. Prunotto M, Carnevali ML, Candiano G, Murtas C, Bruschi M. Autoimmunity in membranous nephropathy targets aldose reductase and SOD2. J Am Soc Nephrol. 2010; 21: 507-519.

25. Debiec H, Ronco P. Immunopathogenesis of membranous nephropathy: an update. Semin Immunopathol. 2014; 36: 381-397.

26. Finkielman JD, Lee AS, Hummel AM, Viss MA, Jacob GL. ANCA are detectable in nearly all patients with active severe Wegener's granulomatosis. Am J Med. 2007; 120: 643.

27. Saadoun D, Resche Rigon M, Sene D, Terrier B, Karras A. Rituximab plus Peg-interferon-alpha/ribavirin compared with Peg-interferon-alpha/ribavirin in hepatitis C-related mixed cryoglobulinemia. Blood. 2010; 116: 326-334.

28. Condon MB, Ashby D, Pepper RJ, Cook HT, Levy JB. Prospective observational single-centre cohort study to evaluate the effectiveness of treating lupus nephritis with rituximab and mycophenolate mofetil but no oral steroids. Ann Rheum Dis. 2013; 72: 1280-1286.

29. Syeda UA, Singer NG, Magrey M. Anti-glomerular basement membrane antibody disease treated with rituximab: A case-based review. Semin Arthritis Rheum. 2013; 42: 567-572.

30. Colvin RB, Smith RN. Antibody-mediated organ-allograft rejection. Nat Rev Immunol. 2005; 5: 807-817.

31. Einecke G, Sis B, Reeve J, Mengel M, Campbell PM. Antibody-mediated microcirculation injury is the major cause of late kidney transplant failure. Am J Transplant. 2009; 9: 2520-2531.

32. Sis B, Mengel M, Haas M, Colvin RB, Halloran PF. Banff '09 meeting report: antibody mediated graft deterioration and implementation of Banff working groups. Am J Transplant. 2010; 10: 464-471.

33. Sanders JS, Abdulahad WH, Stegeman CA, Kallenberg CG. Pathogenesis of antineutrophil cytoplasmic autoantibody-associated vasculitis and potential targets for biologic treatment. Nephron Clin Pract. 2014; 128: 216-223.

34. Abdulahad WH, Lamprecht P, Kallenberg CG. T-helper cells as new players in ANCA-associated vasculitides. Arthritis Res Ther. 2011; 13: 236.

35. McKinney EF, Willcocks LC, Broecker V, Smith KG. The immunopathology of ANCA-associated vasculitis. Semin Immunopathol. 2014; 36: 461-478.

36. Liu Y, Anders HJ. Lupus nephritis: from pathogenesis to targets for biologic treatment. Nephron Clin Pract. 2014; 128: 224-231.

37. Mak A, Kow NY. The pathology of T cells in systemic lupus erythematosus. J Immunol Res. 2014; 2014: 419029.

38. Zhang Q, Luan H, Wang L, He F, Zhou H. Galectin-9 ameliorates anti-GBM glomerulonephritis by inhibiting Th1 and Th17 immune responses in mice. Am J Physiol Renal Physiol. 2014; 306: F822-832.

39. Inoshita H, Kim BG, Yamashita M, Choi SH, Tomino Y. Disruption of Smad4 expression in T cells leads to IgA nephropathy-like manifestations. PLoS One. 2013; 8: e78736.

40. Van der Touw W, Bromberg JS. Natural killer cells and the immune response in solid organ transplantation. Am J Transplant. 2010; 10: 1354-1358.

41. Joy MS, Gipson DS, Powell L, MacHardy J, Jennette JC, et al. Phase 1 trial of adalimumab in Focal Segmental Glomerulosclerosis (FSGS): II. Report of the FONT (Novel Therapies for Resistant FSGS) study group. Am J Kidney Dis. 2010; 55: 50-60.

42. Booth A, Harper L, Hammad T, Bacon P, Griffith M. Prospective study of TNFalpha blockade with infliximab in anti-neutrophil cytoplasmic antibody-associated systemic vasculitis. J Am Soc Nephrol. 2004; 15: 717-721.

43. Wegener's Granulomatosis Etanercept Trial (WGET) Research Group. Etanercept plus standard therapy for Wegener's granulomatosis. N Engl J Med. 2005; 352: 351-361.

44. Michaelson JS, Wisniacki N, Burkly LC, Putterman C. Role of TWEAK in lupus nephritis: a bench-to-bedside review. J Autoimmun. 2012; 39: 130-142.

45. McIntosh LM, Barnes JL, Barnes VL, McDonald JR. Selective CCR2-targeted macrophage depletion ameliorates experimental mesangioproliferative glomerulonephritis. Clin Exp Immunol. 2009; 155: 295-303.

46. Cherukuri A, Rothstein DM, Clark B, Carter CR, Davison A. Immunologic human renal allograft injury associates with an altered IL-10/TNF-Î± expression ratio in regulatory B cells. J Am Soc Nephrol. 2014; 25: 1575-1585.

47. Wu D, Liu X, Liu C, Liu Z, Xu M. Network analysis reveals roles of inflammatory factors in different phenotypes of kidney transplant patients. J Theor Biol. 2014; 362: 62-68.

48. Naujokat C, Berges C, Fuchs D, Sadeghi M, Opelz G. Antithymocyte globulins suppress dendritic cell function by multiple mechanisms. Transplantation. 2007; 83: 485-497.

49. Beiras-Fernandez A, Chappell D, Hammer C, Beiras A, Reichart B. Impact of polyclonal anti-thymocyte globulins on the expression of adhesion and inflammation molecules after ischemia-reperfusion injury. Transpl Immunol. 2009; 20: 224-228.

50. Available on https://clinicaltrials.gov Identifier NCT01794663 accessed by March 30th , 2016

51. Zhao H, Perez JS, Lu K, George AJ, Ma D. Role of Toll-like receptor-4 in renal graft ischemia-reperfusion injury. Am J Physiol Renal Physiol. 2014; 306: F801-811.

52. Xue C, Liu Y, Li C, Li Y, Yang T. Powerful protection against renal ischemia reperfusion injury by T cell-specific NF-ÎºB inhibition. Transplantation. 2014; 97: 391-396.

53. Coppo R, Camilla R, Alfarano A, Balegno S, Mancuso D. Upregulation of the immunoproteasome in peripheral blood mononuclear cells of patients with IgA nephropathy. Kidney Int. 2009; 75: 536-541.

54. Sahali D, Pawlak A, Le Gouvello S, Lang P, Valanciuté A. Transcriptional and post-transcriptional alterations of IkappaBalpha in active minimal-change nephrotic syndrome. J Am Soc Nephrol. 2001; 12: 1648-1658.

55. Popat RJ, Robson MG. Complement and glomerular diseases. Nephron Clin Pract. 2014; 128: 238-242.

56. Salvadori M, Rosso G, Bertoni E. Complement involvement in kidney diseases: From physiopathology to therapeutical targeting. World J Nephrol. 2015; 4: 169-184.

57. Available on https://clinicaltrials.gov : Eculizumab in renal diseases. Accessed by March 30th, 2016.

58. Available on https://clinicaltrials.gov : Eculizumab in renal transplantation. Accessed by March 30th, 2016.

59. Zuber J, Fakhouri F, Roumenina LT, Loirat C, Frémeaux-Bacchi V; French Study Group for aHUS/C3G. Use of eculizumab for atypical haemolytic uraemic syndrome and C3 glomerulopathies. Nat Rev Nephrol. 2012; 8: 643-657.

60. Legendre CM, Licht C, Muus P, Greenbaum LA, Babu S. Terminal complement inhibitor eculizumab in atypical hemolytic-uremic syndrome. N Engl J Med. 2013; 368: 2169-2181.

61. Kielstein JT, Beutel G, Fleig S, Steinhoff J, Meyer TN. Best supportive care and therapeutic plasma exchange with or without eculizumab in Shiga-toxin-producing E. coli O104: H4 induced haemolytic-uraemic syndrome: an analysis of the German STEC-HUS registry. Nephrol Dial Transplant. 2012; 27: 3807-3815.

62. Delmas Y, Vendrely B, Clouzeau B, Bachir H, Bui HN. Outbreak of Escherichia coli O104: H4 haemolytic uraemic syndrome in France: outcome with eculizumab. Nephrol Dial Transplant. 2014; 29: 565-572.

63. Radhakrishnan S, Lunn A, Kirschfink M, Thorner P, Hebert D. Eculizumab and refractory membrano proliferative glomerulonephritis. N Engl J Med. 2012; 366: 1165-1166.

64. Vivarelli M, Pasini A, Emma F. Eculizumab for the treatment of dense-deposit disease. N Engl J Med. 2012; 366: 1163-1165.

65. Daina E, Noris M, Remuzzi G. Eculizumab in a patient with dense-deposit disease. N Engl J Med. 2012; 366: 1161-1163.

66. McCaughan JA, O'Rourke DM, Courtney AE. Recurrent dense deposit disease after renal transplantation: an emerging role for complementary therapies. Am J Transplant. 2012; 12: 1046-1051.

67. Kerns E, Rozansky D, Troxell ML. Evolution of immunoglobulin deposition in C3-dominant membranoproliferative glomerulopathy. Pediatr Nephrol. 2013; 28: 2227-2231.

68. Gurkan S, Fyfe B, Weiss L, Xiao X, Zhang Y. Eculizumab and recurrent C3 glomerulonephritis. Pediatr Nephrol. 2013; 28: 1975-1981.

69. Bomback AS, Smith RJ, Barile GR, Zhang Y, Heher EC. Eculizumab for dense deposit disease and C3 glomerulonephritis. Clin J Am Soc Nephrol. 2012; 7: 748-756.

70. Available on https://clinicaltrials.gov. Identifiers: NCT01919346, NCT02145182, NCT01756508. Accessed by March 30th, 2016.

71. Zuber J, Le Quintrec M, Krid S, Bertoye C, Gueutin V. Eculizumab for atypical hemolytic uremic syndrome recurrence in renal transplantation. Am J Transplant. 2012; 12: 3337-3354.

72. Lonze BE, Dagher NN, Simpkins CE, Locke JE, Singer AL. Eculizumab, bortezomib and kidney paired donation facilitate transplantation of a highly sensitized patient without vascular access. Am J Transplant. 2010; 10: 2154-2160.

73. Cohney SJ, Hughes P, Rosemary M, Walker RG, Cantwell L, et al. C5 inhibition with eculizumab to prevent antibody mediated rejection (AbMR) in patients with donor specific anti-HLA antibody (DSAb) and a positive cross match. Am J Transplant 11. 2011; S2: 483.

74. Hardinger KL, Brennan DC. Novel immunosuppressive agents in kidney transplantation. World J Transplant. 2013; 3: 68-77.

75. Stegall MD, Diwan T, Raghavaiah S, Cornell LD, Burns J. Terminal complement inhibition decreases antibody-mediated rejection in sensitized renal transplant recipients. Am J Transplant. 2011; 11: 2405-2413.

76. Available on https://clinicaltrials.gov. Identifier NCT01363388 accessed by March 30th, 2016.

77. Ricklin D, Lambris JD. Complement in immune and inflammatory disorders: therapeutic interventions. J Immunol. 2013; 190: 3839-3847.

78. Cravedi P, Leventhal J, Lakhani P, Ward SC, Donovan MJ. Immune cell-derived C3a and C5a costimulate human T cell alloimmunity. Am J Transplant. 2013; 13: 2530-2539.

79. Woodruff TM, Nandakumar KS, Tedesco F. Inhibiting the C5-C5a receptor axis. Mol Immunol. 2011; 48: 1631-1642.

80. Li R, Coulthard LG, Wu MC, Taylor SM, Woodruff TM. C5L2: a controversial receptor of complement anaphylatoxin, C5a. FASEB J. 2013; 27: 855-864.

81. Huugen D, van Esch A, Xiao H, Peutz-Kootstra CJ, Buurman WA. Inhibition of complement factor C5 protects against anti-myeloperoxidase antibody-mediated glomerulonephritis in mice. Kidney Int. 2007; 71: 646-654.

82. Xiao H, Dairaghi DJ, Powers JP, Ertl LS, Baumgart T. C5a receptor (CD88) blockade protects against MPO-ANCA GN. J Am Soc Nephrol. 2014; 25: 225-231.

83. Fang Y, Xu C, Fu YX, Holers VM, Molina H. Expression of complement receptors 1 and 2 on follicular dendritic cells is necessary for the generation of a strong antigen-specific IgG response. J Immunol. 1998; 160: 5273-5279.

84. Rødgaard A, Christensen LD, Thomsen BS, Wiik A, Bendixen G. Complement receptor type 1 (CR1, CD35) expression on peripheral T lymphocytes: both CD4- and CD8-positive cells express CR1. Complement Inflamm. 1991; 8: 303-309.

85. Weiss L, Fischer E, Haeffner-Cavaillon N, Jouvin MH, Appay MD. The human C3b receptor (CR1). Adv Nephrol Necker Hosp. 1989; 18: 249-269.

86. Zhang Y, Nester CM, Holanda DG, Marsh HC, Hammond RA. Soluble CR1 therapy improves complement regulation in C3 glomerulopathy. J Am Soc Nephrol. 2013; 24: 1820-1829.

87. Available on https://clinicaltrials.gov Identifier NCT 01791686. Accessed by March 30th, 2016.

88. Sacks S, Karegli J, Farrar CA, Asgari E, Schwaeble W. Targeting complement at the time of transplantation. Adv Exp Med Biol. 2013; 735: 247-255.

89. Available on http://www.controlled-trials.com/ISRCTN49958194, accessed by March 30st, 2016.

90. Fridkis-Hareli M, Storek M, Mazsaroff I, Risitano AM, Lundberg AS. Design and development of TT30, a novel C3d-targeted C3/C5 convertase inhibitor for treatment of human complement alternative pathway-mediated diseases. Blood. 2011; 118: 4705-4713.

91. Available on https://clinicaltrials.gov Identifiers: NCT01134510, NCT01147302, NCT02134314 accessed by March 30th , 2016.

92. Jones RB, Ferraro AJ, Chaudhry AN, Brogan P, Salama AD. A multicenter survey of rituximab therapy for refractory antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum. 2009; 60: 2156-2168.

93. Jones RB. Rituximab in the treatment of anti-neutrophil cytoplasm antibody-associated vasculitis. Nephron Clin Pract. 2014; 128: 243-249.

94. Little MA, Al-Ani B, Ren S, Al-Nuaimi H, Leite M Jr. Anti-proteinase 3 anti-neutrophil cytoplasm autoantibodies recapitulate systemic vasculitis in mice with a humanized immune system. PLoS One. 2012; 7: e28626.

95. Voswinkel J, Müller A, Lamprecht P. Is PR3-ANCA formation initiated in Wegener's granulomatosis lesions? Granulomas as potential lymphoid tissue maintaining autoantibody production. Ann N Y Acad Sci. 2005; 1051: 12-19.

96. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med. 2010; 363: 221-232.

97. Jones RB, Tervaert JW, Hauser T, Luqmani R, Morgan MD. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med. 2010; 363: 211-220.

98. Available on https://clinicaltrials.gov Identifier NCT00987389 accessed by March 30th, 2016

99. Available on https://clinicaltrials.gov Identifier NCT01697267 accessed by March 30th, 2016

100. Guillevin L1, Pagnoux C, Karras A, Khouatra C, Aumaître O. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. N Engl J Med. 2014; 371: 1771-1780.

101. Available on https://clinicaltrials.gov Identifier NCT01731561 accessed by March 30th, 2016.

102. Available on https://clinicaltrials.gov Identifier NCT00275613 accessed by March 30th , 2016

103. Ruggenenti P, Chiurchiu C, Abbate M, Perna A, CravediP. Rituximab for idiopathic membranous nephropathy: who can benefit? Clin J Am Soc Nephrol. 2006; 1: 738-748.

104. Bomback AS, Derebail VK, McGregor JG, Kshirsagar AV, Falk RJ. Rituximab therapy for membranous nephropathy: a systematic review.Clin J Am Soc Nephrol. 2009; 4: 734-744.

105. Fervenza FC, Abraham RS, Erickson SB, Irazabal MV, Eirin A, et al. Mayo Nephrology Collaborative Group Rituximab therapy in idiopathic membranous nephropathy: a 2-year study. Clin J Am Soc Nephrol. 2010; 5: 2188-2198.

106. Fervenza FC, Cosio FG, Erickson SB, Specks U, Herzenberg AM. Rituximab treatment of idiopathic membranous nephropathy. Kidney Int. 2008; 73: 117-125.

107. Ruggenenti P, Cravedi P, Chianca A, Perna A, Ruggiero B. Rituximab in idiopathic membranous nephropathy. J Am Soc Nephrol. 2012; 23: 1416-1425.

108. Beck LH, Fervenza FC, Beck DM, Bonegio RG, Malik FA. Rituximab-induced depletion of anti-PLA2R autoantibodies predicts response in membranous nephropathy. J Am Soc Nephrol. 2011; 22: 1543-1550.

109. Rituximab for membranous nephropathy. Available on https://clinicaltrials.gov: rituximab for membranous nephropathy; accessed by March 30th , 2016

110. Rovin BH, Furie R, Latinis K, Looney RJ, Fervenza FC. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study. Arthritis Rheum. 2012; 64: 1215-1226.

111. Lightstone L. The landscape after LUNAR: rituximab's crater-filled path. Arthritis Rheum. 2012; 64: 962-965.

112. Condon MB, Ashby D, Pepper RJ, Cook HT, Levy JB. Prospective observational single-centre cohort study to evaluate the effectiveness of treating lupus nephritis with rituximab and mycophenolate mofetil but no oral steroids. Ann Rheum Dis. 2013; 72: 1280-1286.

113. Available on https://clinicaltrials.gov Identifier NCT01673295 accessed by March 30th ,2016

114. Rituximab for lupus nephritis. Available on https://clinicaltrials.gov: rituximab for lupus nephritis; accessed by March 30th , 2016

115. Javaugue V, Karras A, Glowacki F, McGregor B, Lacombe C. Long-term kidney disease outcomes in fibrillary glomerulonephritis: a case series of 27 patients. Am J Kidney Dis. 2013; 62: 679-690.

116. Available on https://clinicaltrials.gov Identifier NCT00498368 accessed by March 30th, 2016

117. Kronbichler A, Bruchfeld A. Rituximab in adult minimal change disease and focal segmental glomerulosclerosis. Nephron Clin Pract. 2014; 128: 277-282.

118. Kronbichler A, Kerschbaum J, Fernandez-Fresnedo G, Hoxha E, Kurschat CE. Rituximab treatment for relapsing minimal change disease and focal segmental glomerulosclerosis: a systematic review. Am J Nephrol. 2014; 39: 322-330.

119. Rituximab for FSGS. Rituximab for focal segmental glomeruloscerosis; accessed, 2016.

120. Grenda R. Biologics in renal transplantation. Pediatr Nephrol. 2015; 30: 1087-1098.

121. Macklin PS, Morris PJ, Knight SR. A systematic review of the use of rituximab for desensitization in renal transplantation. Transplantation. 2014; 98: 794-805.

122. Roberts DM, Jiang SH, Chadban SJ. The treatment of acute antibody-mediated rejection in kidney transplant recipients-a systematic review. Transplantation. 2012; 94: 775-783.

123. Available on https://clinicaltrials.gov Identifiers NCT01117662, NCT00476164, NCT00568477.Accessed by March 30th , 2016

124. Available on https://clinicaltrials.gov Identifier NCT00626197.Accessed by March 30th, 2016.

125. Mysler EF, Spindler AJ, Guzman R, Bijl M, Jayne D. Efficacy and safety of ocrelizumab in active proliferative lupus nephritis: results from a randomized, double-blind, phase III study. Arthritis Rheum. 2013; 65: 2368-2379.

126. Available on https://clinicaltrials.gov Identifier NCT01405807 accessed by March 30th , 2016.

127. Alemtuzumab in renal transplant. Available on https://clinicaltrials.gov: alemtuzumab in renal transplantation; accessed by March 30th , 2016

128. Haynes R, Harden P, Judge P, Blackwell L, Emberson. (2014) 3C Study Collaborative Group Alemtuzumab-based induction treatment versus basiliximab-based induction treatment in kidney transplantation (the 3C Study): a randomised trial. Lancet. 2014; 384: 1684-1690.

129. Friend PJ. Alemtuzumab induction therapy in solid organ transplantation. Transplant Res. 2013; 2: S5.

130. Noureldeen T, Albekioni Z, Machado L, Muddana N, Marcus RJ. Alemtuzumab induction and antibody-mediated rejection in kidney transplantation. Transplant Proc. 2014; 46: 3405-3407.

131. Upadhyay K, Midgley L, Moudgil A. Safety and efficacy of alemtuzumab in the treatment of late acute renal allograft rejection. Pediatr Transplant. 2012; 16: 286-293.

132. Available on https://clinicaltrials.gov Identifier NCT01845740 accessed by March 30th , 2016.

133. Available on https://clinicaltrials.gov Identifier NCT01103778 accessed by March 30th , 2016.

134. Available on https://clinicaltrials.gov Identifier NCT01169857 accessed by March 30th , 2016.

135. Everly MJ, Terasaki PI, Trivedi HL. Durability of antibody removal following proteasome inhibitor-based therapy Transplantation. 2012; 93: 572-577.

136. Bortezomib in renal transplant. Available on https://clinicaltrials.gov: bortezomib in renal transplantation; accessed by March 30th, 2016.

137. Available on https://clinicaltrials.gov Identifiers NCT02201576, NCT01873157 accessed by March 30th, 2016.

138. Manzi S, Sánchez-Guerrero J, Merrill JT, Furie R, Gladman D. BLISS-52 and BLISS-76 Study Groups. Effects of belimumab, a B lymphocyte stimulator-specific inhibitor, on disease activity across multiple organ domains in patients with systemic lupus erythematosus: combined results from two phase III trials. Ann Rheum Dis. 2012; 71: 1833-1838.

139. Dooley MA, Houssiau F, Aranow C, D'Cruz DP, Askanase A. Effect of belimumab treatment on renal outcomes: results from the phase 3 belimumab clinical trials in patients with SLE. Lupus. 2013; 22: 63-72.

140. Available on https://clinicaltrials.gov Identifiers NCT01639339, NCT02260934; accessed by March 30th , 2016

141. Available on https://clinicaltrials.gov Identifier NCT01610492; accessed by March 30th, 2016

142. Available on https://clinicaltrials.gov Identifier NCT01663623; accessed by March 30th, 2016.

143. Webber A, Hirose R, Vincenti F. Novel strategies in immunosuppression: issues in perspective. Transplantation. 2011; 91: 1057-1064.

144. Available on https://clinicaltrials.gov Identifier NCT01536379; accessed by March 30th, 2016.

145. Available on https://clinicaltrials.gov Identifiers NCT01196091, NCT01488708; accessed by March 30th, 2016.

146. Available on https://clinicaltrials.gov Identifiers NCT02074020, NCT02052219; accessed by March 30th, 2016.

147. Ramanujam M, Wang X, Huang W, Liu Z, Schiffer L. Similarities and differences between selective and nonselective BAFF blockade in murine SLE. J Clin Invest. 2006; 116: 724-734.

148. Ginzler EM, Wax S, Rajeswaran A, Copt S, Hillson J. Atacicept in combination with MMF and corticosteroids in lupus nephritis: results of a prematurely terminated trial. Arthritis Res Ther. 2012; 14: R33.

149. Wallace DJ, Kalunian K, Petri MA, Strand V, Houssiau FA. Efficacy and safety of epratuzumab in patients with moderate/severe active systemic lupus erythematosus: results from EMBLEM, a phase IIb, randomised, double-blind, placebo-controlled, multicentre study. Ann Rheum Dis. 2014; 73: 183-190.

150. Jordan SC, Toyoda M, Vo AA. Intravenous immunoglobulin a natural regulator of immunity and inflammation. Transplantation. 2009; 88: 1-6.

151. Jordan SC. Treatment of systemic and renal-limited vasculitic disorders with pooled human intravenous immune globulin. J Clin Immunol. 1995; 15: 76S-85S.

152. Rasche FM, Keller F, Lepper PM, Aymanns C, Karges W. High-dose intravenous immunoglobulin pulse therapy in patients with progressive immunoglobulin A nephropathy: a long-term follow-up. Clin Exp Immunol. 2006; 146: 47-53.

153. Endo LM, Giannobile JV, Dobbs AK, Foote JB, Szymanska E. Membranous glomerulopathy in an adult patient with X-linked a gammaglobulinemia receiving intravenous gammaglobulin. J Investig Allergol Clin Immunol. 2011; 21: 405-409.

154. Available on https://clinicaltrials.gov Identifier NCT00699140; accessed by March 30th, 2016.

155. Garonzik Wang JM, Montgomery RA, Kucirka LM, Berger JC, Warren DS. Incompatible live-donor kidney transplantation in the United States: results of a national survey. Clin J Am Soc Nephrol. 2011; 6: 2041-2046.

156. Vo AA, Lukovsky M, Toyoda M, Wang J, Reinsmoen NL. Rituximab and intravenous immune globulin for desensitization during renal transplantation. N Engl J Med. 2008; 359: 242-251.

157. IVIG in renal transplant. Available on https://clinicaltrials.gov: IVIG in renal transplantation; accessed by March 30th, 2016.

158. Billing H, Rieger S, Ovens J, Süsal C, Melk A. Successful treatment of chronic antibody-mediated rejection with IVIG and rituximab in pediatric renal transplant recipients. Transplantation. 2008; 8: 1214-1221.

159. Billing H, Rieger S, Süsal C, Waldherr R, Opelz G. IVIG and rituximab for treatment of chronic antibody-mediated rejection: a prospective study in paediatric renal transplantation with a 2-year follow-up. Transpl Int. 2012; 25: 1165-1173.

160. Webster AC, Ruster LP, McGee R, Matheson SL, Higgins GY. Interleukin 2 receptor antagonists for kidney transplant recipients. Cochrane Database Syst Rev. 2010; CD003897.

161. Grenda R, Watson A, Vondrak K, Webb NJ, Beattie J. A prospective, randomized, multicenter trial of tacrolimus-based therapy with or without basiliximab in pediatric renal transplantation. Am J Transplant. 2006; 6: 1666-1672.

162. Offner G, Toenshoff B, Höcker B, Krauss M, Bulla M. Efficacy and safety of basiliximab in pediatric renal transplant patients receiving cyclosporine, mycophenolate mofetil, and steroids. Transplantation. 2008; 86: 1241-1248.

163. Grenda R. Steroid withdrawal in renal transplantation. Pediatr Nephrol. 2013; 28: 2107-2112.

164. Available on https://clinicaltrials.gov Identifier NCT01544491; accessed by March 30th, 2016.

165. Hardinger KL, Brennan DC, Schnitzler MA. Rabbit antithymocyte globulin is more beneficial in standard kidney than in extended donor recipients. Transplantation. 2009; 87: 1372-1376.

166. Hardinger KL, Schnitzler MA, Miller B, Lowell JA, Shenoy S. Five-year follows up of thymoglobulin versus ATGAM induction in adult renal transplantation. Transplantation. 2004; 78: 136-141.

167. Mourad G, Garrigue V, Squifflet JP, Besse T, Berthoux F. Induction versus non induction in renal transplant recipients with tacrolimus-based immunosuppression. Transplantation. 2001; 72: 1050-1055.

168. Charpentier B, Rostaing L, Berthoux F, Lang P, Civati G. A three-arm study comparing immediate tacrolimus therapy with antithymocyte globulin induction therapy followed by tacrolimus or cyclosporine A in adult renal transplant recipients. Transplantation. 2003; 75: 844-851.

169. Liu Y, Zhou P, Han M, Xue CB, Hu XP. Basiliximab or antithymocyte globulin for induction therapy in kidney transplantation: a meta-analysis. Transplant Proc. 2010; 42: 1667-1670.

170. Brennan DC, Schnitzler MA. Long-term results of rabbit antithymocyte globulin and basiliximab induction. N Engl J Med. 2008; 359: 1736-1738.

171. Bashir SJ, Maibach HI. Alefacept (Biogen). Curr Opin Investig Drugs. 2001; 2: 631-634.

172. Astellas. (2009-12-15). "Voluntary US Market Discontinuatioof Amevive (alefacept)". Press release.

173. Rostaing L, Charpentier B, Glyda M, Rigotti P, Hettich F. Alefacept combined with tacrolimus, mycophenolate mofetil and steroids in de novo kidney transplantation: a randomized controlled trial. Am J Transplant. 2013; 13: 1724-1733.

174. Genentech, Inc. (2009-04-08). "Genentech Announces Voluntary Withdrawal of Raptiva from the U.S. Market". Press release.

175. Vincenti F, Mendez R, Pescovitz M, Rajagopalan PR, Wilkinson AH. A phase I/II randomized open-label multicenter trial of efalizumab, a humanized anti-CD11a, anti-LFA-1 in renal transplantation. Am J Transplant. 2007; 7: 1770-1777.

176. Kanmaz T, Fechner JJ Jr, Torrealba J, Kim HT, Dong Y. Monotherapy with the novel human anti-CD154 monoclonal antibody ABI793 in rhesus monkey renal transplantation model. Transplantation. 2004; 77: 914-920.

177. Larsen CP, Knechtle SJ, Adams A, Pearson T, Kirk AD. A new look at blockade of T-cell costimulation: a therapeutic strategy for long-term maintenance immunosuppression. Am J Transplant. 2006; 6: 876-883.

178. Okimura K, Maeta K, Kobayashi N, Goto M, Kano N. Characterization of ASKP1240, a fully human antibody targeting human CD40 with potent immunosuppressive effects. Am J Transplant. 2014; 14: 1290-1299.

179. Available on https://clinicaltrials.gov Identifiers NCT01780844, NCT01279538; accessed by March 30th, 2016

180. Wéclawiak H, Kamar N, Ould-Mohamed A, Cardeau-Desangles I, Rostaing L. Biological agents in kidney transplantation: belatacept is entering the field. Expert Opin Biol Ther. 2010; 10: 1501-1508.

181. Furie R, Nicholls K, Cheng TT, Houssiau F, Burgos-Vargas R. Efficacy and safety of abatacept in lupus nephritis: a twelve-month, randomized, double-blind study. Arthritis Rheumatol. 2014; 66: 379-389.

182. Available on https://clinicaltrials.gov Identifiers NCT00705367, NCT00094380, NCT01714817; accessed by March 30th 2016.

183. Available on https://clinicaltrials.gov Identifier NCT00468208; accessed by March 30th, 2016.

184. Available on https://clinicaltrials.gov Identifier NCT00774852; accessed by March 30th, 2016.

185. Yu CC, Fornoni A, Weins A, Hakroush S, Maiguel D. Abatacept in B7-1-positive proteinuric kidney disease. N Engl J Med. 2013; 369: 2416-2423.

186. Rostaing L, Vincenti F, Grinyó J, Rice KM, Bresnahan B. Long-term belatacept exposure maintains efficacy and safety at 5 years: results from the long-term extension of the BENEFIT study. Am J Transplant. 2013; 13: 2875-2883.

187. Charpentier B, Medina Pestana JO, Del C Rial M, Rostaing L, Grinyó J. Long-term exposure to belatacept in recipients of extended criteria donor kidneys. Am J Transplant. 2013; 13: 2884-2891.

188. Masson P, Henderson L, Chapman JR, Craig JC, Webster AC. Belatacept for kidney transplant recipients. Cochrane Database Syst Rev. 2014; 11: CD010699.

189. Available on https://clinicaltrials.gov Identifiers NCT01837043, NCT02134288; accessed by March 30th, 2016.

190. Available on https://clinicaltrials.gov Identifier NCT00402168; accessed by March 30th, 2016.

191. Available on https://clinicaltrials.gov Identifier NCT01791491; accessed by March 30th, 2016.

192. Nakamura T, Higashi S, Tomoda K, Tsukano M, Shono M. Effectiveness of etanercept *vs.* cyclophosphamide as treatment for patients with amyloid A amyloidosis secondary to rheumatoid arthritis. Rheumatology (Oxford). 2012; 51: 2064-2069.

193. Available on https://clinicaltrials.gov Identifiers NCT00814255, NCT00193648; accessed by March 30th, 2016.

194. Aringer M, Houssiau F, Gordon C, Graninger WB, Voll RE. Adverse events and efficacy of TNF-alpha blockade with infliximab in patients with systemic lupus erythematosus: long-term follow-up of 13 patients. Rheumatology (Oxford). 2009; 48: 1451-1454.

195. Available on https://clinicaltrials.gov Identifier NCT00753103; accessed by April 17th, 2016.

196. Available on https://clinicaltrials.gov Identifiers NCT00447265; accessed by March 30th, 2016.

197. Available on https://clinicaltrials.gov Identifiers NCT00144573, NCT01273389, NCT02349061; accessed by March 30th, 2016.

198. Available on https://clinicaltrials.gov Identifier NCT01499355; accessed by March 30th, 2016.

199. Kalunian KC, Merrill JT, Maciuca R, McBride JM, Townsend MJ. A Phase II study of the efficacy and safety of rontalizumab (rhuMAb interferon-Î±) in patients with systemic lupus erythematosus (ROSE). Ann Rheum Dis. 2016; 75: 196-202.

200. Petri M, Wallace DJ, Spindler A, Chindalore V, Kalunian K. Sifalimumab, a human anti-interferon-Î± monoclonal antibody, in systemic lupus erythematosus: a phase I randomized, controlled, dose-escalation study. Arthritis Rheum. 2013; 65: 1011-1021.

201. Tcherepanova I, Curtis M, Sale M, Miesowicz F, Nicolette C. Results of a randomized placebo controlled phase IA study of AGS-009, a humanized anti-interferon-a monoclonal antibody in subjects with systemic lupus erythematosus. Ann Rheum Dis. 2012; 71: 536.

202. Available on https://clinicaltrials.gov Identifier NCT00818948; accessed by March 30th, 2016.

203. Lauwerys BR, Hachulla E, Spertini F, Lazaro E, Jorgensen C. Down-regulation of interferon signature in systemic lupus erythematosus patients by active immunization with interferon Î±-kinoid. Arthritis Rheum. 2013; 65: 447-456.

204. Available on https://clinicaltrials.gov Identifier NCT01058343; accessed by March 30th, 2016.

205. Available on https://clinicaltrials.gov Identifier NCT01438489; accessed by April 18th, 2016.

206. Available on https://clinicaltrials.gov Identifier NCT01541670; accessed by March 30th, 2016.

207. Available on https://clinicaltrials.gov Identifier NCT00856674; accessed by March 30th, 2016.

208. Kulkarni O, Eulberg D, Selve N, Zöllner S, Allam R. Anti-Ccl2 Spiegelmer permits 75% dose reduction of cyclophosphamide to control diffuse proliferative lupus nephritis and pneumonitis in MRL-Fas(lpr) mice. J Pharmacol Exp Ther. 2009; 328: 371-377.

209. Ble A, Mosca M, Di Loreto G, Guglielmotti A, Biondi G. Antiproteinuric effect of chemokine C-C motif ligand 2 inhibition in subjects with acute proliferative lupus nephritis. Am J Nephrol. 2011; 34: 367-372.

210. Solhjou Z, Athar H, Xu Q, Abdi R. Emerging therapies targeting intra-organ inflammation in transplantation. Am J Transplant. 2015; 15: 305-311.

211. Hanidziar D, Koulmanda M. Inflammation and the balance of Treg and Th17 cells in transplant rejection and tolerance. Curr Opin Organ Transplant. 2010; 15: 411-415.

212. Wang X, Xu X, Huang H, Cai M, Qian Y. Interleukin-6 first plays pro- then anti-inflammatory role in early versus late acute renal allograft rejection. Ann Clin Lab Sci. 2013; 43: 389-394.

213. Jones SA, Fraser DJ, Fielding CA, Jones GW. Interleukin-6 in renal disease and therapy. Nephrol Dial Transplant. 2015; 30: 564-574.

214. Van Oers MH, Van der Heyden AA, Aarden LA. Interleukin 6 (IL-6) in serum and urine of renal transplant recipients. Clin Exp Immunol. 1988; 71: 314-319.

215. Casiraghi F, Ruggenenti P, Noris M, Locatelli G, Perico N. Sequential monitoring of urine-soluble interleukin 2 receptor and interleukin 6 predicts acute rejection of human renal allografts before clinical or laboratory signs of renal dysfunction. Transplantation. 1997; 63: 1508-1514.

216. Hernandez-Alejandro R, Zhang X, Croome KP, Zheng X, Parfitt J. Reduction of liver ischemia reperfusion injury by silencing of TNF-Î± gene with shRNA. J Surg Res. 2012; 176: 614-620.

217. Pascher A, Klupp J. Biologics in the treatment of transplant rejection and ischemia/reperfusion injury: new applications for TNFalpha inhibitors? BioDrugs. 2005; 19: 211-231.

218. Izawa A, Ueno T, Jurewicz M, Ito T, Tanaka K. Importance of donor- and recipient-derived selectins in cardiac allograft rejection. J Am Soc Nephrol. 2007; 18: 2929-2936.

219. Shapiro AM. State of the art of clinical islet transplantation and novel protocols of immunosuppression. Curr Diab Rep. 2011; 11: 345-354.

220. McCall M, Shapiro AM. Update on islet transplantation. Cold Spring Harb Perspect Med. 2012; 2: a007823.

221. Chhabra P, Brayman KL. Current status of immunomodulatory and cellular therapies in preclinical and clinical islet transplantation. J Transplant. 2011; 2011: 637692.

222. Available on https://clinicaltrials.gov Identifiers: NCT02464878; NCT02713997; NCT00468117; accessed by March 30th , 2016

223. McCall M, Pawlick R, Kin T, Shapiro AM. Anakinra potentiates the protective effects of etanercept in transplantation of marginal mass human islets in immuno deficient mice. Am J Transplant. 2012; 12: 322-329.

224. https://clinicaltrials.gov Identifiers: NCT01346085; accessed by March 30th, 2016.

225. Available on https://clinicaltrials.gov Identifier NCT01594424; accessed by March 30th, 2016.

226. Available on https://clinicaltrials.gov Identifier NCT02108600; accessed by March 30th, 2016.

227. Ho J, Wiebe C, Gibson IW, Hombach-Klonisch S, Gao A. Elevated urinary CCL2: Cr at 6 months is associated with renal allograft interstitial fibrosis and inflammation at 24 months. Transplantation. 2014; 98: 39-46.

228. Campistol JM, Iñigo P, Larios S, Bescos M, Oppenheimer F. Role of transforming growth factor-beta1 in the progression of chronic allograft nephropathy. Nephrol Dial Transplant. 2001; 16: 114-116.

229. Guan Q, Li S, Gao S, Chen H, Nguan CY. Reduction of chronic rejection of renal allografts by anti-transforming growth factor-Î² antibody therapy in a rat model. Am J Physiol Renal Physiol. 2013; 305: F199-207.

230. Luo DD, Phillips A, Fraser D. Bone morphogenetic protein-7 inhibits proximal tubular epithelial cell Smad3 signaling via increased SnoN expression. Am J Pathol. 2010; 176: 1139-1147.

231. Maciel TT, Kempf H, Campos AH. Targeting bone morphogenetic protein signaling on renal and vascular diseases. Curr Opin Nephrol Hypertens. 2010; 19: 26-31.