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

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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 ClinicalTrials.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 ThromboticThrombocytopenic 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.

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

**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.

<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Status</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01756508</td>
<td>Recruiting</td>
<td>Eculizumab for Prevention and Treatment of Kidney Graft Reperfusion Injury</td>
</tr>
<tr>
<td>NCT01919346</td>
<td>Recruiting</td>
<td>Eculizumab for Prevention of DGF in Kidney Transplantation</td>
</tr>
<tr>
<td>NCT02142182</td>
<td>Recruiting</td>
<td>A Trial for Prevention of DGF After Kidney Transplantation</td>
</tr>
<tr>
<td>NCT01567085</td>
<td>Active</td>
<td>Safety and Efficacy of Eculizumab in the Prevention of AMR in Sensitized Recipients of a Kidney Transplant from a Deceased Donor</td>
</tr>
<tr>
<td>NCT01095887</td>
<td>Active</td>
<td>Eculizumab Added to Conventional Treatment in the Prevention of Antibody-mediated Rejection in Blood Group Incompatible Living Donor Kidney Transplantation</td>
</tr>
<tr>
<td>NCT01106027</td>
<td>Active</td>
<td>Dosing Regimen of Eculizumab Added to Conventional Treatment in Positive Crossmatch Deceased Kidney Transplant</td>
</tr>
<tr>
<td>NCT01895127</td>
<td>Recruiting</td>
<td>Efficacy and Safety of Eculizumab for Treatment of Antibody-mediated Rejection Following Renal Transplantation</td>
</tr>
<tr>
<td>NCT010670774</td>
<td>Active</td>
<td>Dosing Regimen of Eculizumab Added to Conventional Treatment in Positive Crossmatch Living Kidney Transplant</td>
</tr>
<tr>
<td>NCT01399593</td>
<td>Active</td>
<td>Safety and Efficacy of Eculizumab to Prevent AMR in Living Donor Kidney Transplant Recipients Receiving Desensitization</td>
</tr>
<tr>
<td>NCT01029587</td>
<td>Recruiting</td>
<td>Eculizumab to Enable Renal Transplantation in Patients with History of Catastrophic Antiphospholipid Antibody Syndrome</td>
</tr>
</tbody>
</table>

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 cyclophosphamide 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 autoantibody-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.

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

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

Table 4: Biologics in LES.

<table>
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<tr>
<th>Target</th>
<th>Drug name</th>
<th>Trial phase</th>
<th>Trial status</th>
<th>Duration, months</th>
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<td>III, IV, V</td>
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<td></td>
<td>ocrelizumab</td>
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<td>Active lupus nephritis</td>
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<tr>
<td>CD74</td>
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<td>recruiting</td>
<td>24</td>
<td>Not specified</td>
<td>NCT01845740</td>
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<tr>
<td>BLys/BAFF</td>
<td>belimumab</td>
<td>3</td>
<td>recruiting</td>
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<td>Active lupus nephritis</td>
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<td>CTLA4</td>
<td>abatacept</td>
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<td>2</td>
<td>SLE</td>
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<tr>
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<td>3</td>
<td>III, IV, V</td>
<td>NCT00094380</td>
</tr>
<tr>
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<td>abatacept</td>
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<td>SLE</td>
<td>NCT00774852</td>
</tr>
<tr>
<td></td>
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<td>III, IV</td>
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</tr>
<tr>
<td>CD40L</td>
<td>Bg9588</td>
<td>2</td>
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<td>5</td>
<td>III, IV</td>
<td>NCT00001789</td>
</tr>
<tr>
<td>IL-6</td>
<td>CNTO136</td>
<td>2</td>
<td>completed</td>
<td>6</td>
<td>III, IV</td>
<td>NCT01273389</td>
</tr>
<tr>
<td></td>
<td>MRA</td>
<td>1</td>
<td>completed</td>
<td>3</td>
<td>Moderately active lupus</td>
<td>NCT00046774</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>AMG811</td>
<td>1</td>
<td>recruiting</td>
<td>6</td>
<td>III, IV</td>
<td>NCT00818948</td>
</tr>
</tbody>
</table>

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.**

<table>
<thead>
<tr>
<th>Rank</th>
<th>Identifier</th>
<th>Status</th>
<th>Patients enrolled</th>
<th>Study name</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>NCT01673295</td>
<td>recruiting</td>
<td>194</td>
<td>RING Rituximab for lupus Nephritis with remission as a Goal</td>
</tr>
<tr>
<td>2</td>
<td>NCT02260934</td>
<td>recruiting</td>
<td>40</td>
<td>Rituximab and Belimumab for Lupus Nephritis</td>
</tr>
<tr>
<td>3</td>
<td>NCT00282347</td>
<td>completed</td>
<td>144</td>
<td>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</td>
</tr>
<tr>
<td>4</td>
<td>NCT01773616</td>
<td>recruiting</td>
<td>252</td>
<td>Trial of Rituximab and Mycophenolate Mofetil Without Oral Steroids for Lupus Nephritis</td>
</tr>
</tbody>
</table>

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].
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.

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

**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 extracellular 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 cyclophosphamide-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 etanercept 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; reanalyzing 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 etanercept 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.

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