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Use of monoclonal antibodies in renal transplantation

Monoclonal antibodies are applied in various settings in renal transplantation. Depleting T-cell antibodies are used for treatment of steroid-resistant acute rejection and as induction therapy to reduce the intensity of concomitant immunosuppressive drug therapy. Induction therapy with the nondepleting IL-2 receptor antagonists basiliximab and daclizumab, added to cyclosporine-based regimens, reduces the incidence of acute rejection without side effects. However, an increase in long-term graft and patient survival has not been demonstrated yet. The B-cell-targeting antibody rituximab is used in blood group ABO-incompatible transplantation, in desensitization protocols, and for treatment of antibody-mediated rejection. Eculizumab interrupts the complement pathway and is a promising tool for the treatment of antibody-mediated rejection and post-transplant hemolytic-uremic syndrome. Future options are monoclonal antibodies with new molecular targets and antibodies that can be used for maintenance immunosuppression in order to avoid the toxicity of existing drugs. However, in several cases, the development of new monoclonal antibodies has been hampered by safety issues.

KEYWORDS: alemtuzumab ■ allograft rejection ■ basiliximab ■ daclizumab ■ eculizumab ■ induction therapy ■ monoclonal antibody ■ muromonab-CD3 ■ rituximab

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For patients with end-stage renal disease, renal transplantation is the treatment of choice to improve quality of life and increase life expectancy. Next to the surgical challenges of this procedure, the manipulation of the alloimmune response is crucial for a successful renal transplantation. The alloimmune response consists of a recognition phase and an effector phase, in which different cells and molecules are involved [1]. Cells that express MHC class II molecules, such as dendritic cells, macrophages and B cells, can act as professional antigen-presenting cells, and thereby stimulate naïve or memory T cells in secondary lymphoid organs. The non-self-HLA molecules of the donor are the major alloantigens. In direct antigen presentation, intact HLA molecules on donor cells are recognized by recipient T cells. Donor HLA molecules can also be indirectly presented to recipient T cells after uptake and processing by antigen-presenting cells of the recipient. In both ways, the T cells recognize the alloantigen in a specific manner via their T-cell receptor. After binding of the alloantigen to the T-cell receptor, a second, costimulatory signal has to be provided by the antigen-presenting cell for optimal T-cell stimulation. The signal from the T-cell receptor–antigen complex and the costimulatory signal provide the initiation of a cascade of different molecular pathways that results in increased

transcription of many proteins, including IL-2. Moreover, upregulation of CD25 (the α -chain of the IL-2 receptor) increases the affinity of the IL-2 receptor for its ligand. Binding of IL-2 to its receptor activates a pathway in which the mTOR is stimulated. This finally leads to progression of cell cycle and cell proliferation and differentiation. Activated CD8⁺ T cells mainly act as cytotoxic T cells, while activated CD4⁺ T cells, also named helper T cells, provide help to CD8⁺ T cells, macrophages and B cells. The effector T cells can be counteracted by regulatory T cells that are derived from the thymus, but can also be induced in the periphery by conversion of other types of T cells. Like T cells, B cells can be activated when they recognize alloantigens with their B-cell receptor. Most B cells need T-cell help for full activation, affinity maturation and immunoglobulin class switching. After differentiation into plasma cells, alloantibodies are produced, of which IgM or immune-complexed IgGs in particular can lead to classical pathway activation of the complement system. This activation will result in cleavage and activation of a cascade of proteins, finally leading to the formation of the membrane attack complex. This complex of proteins can form channels into nearby cells, leading to osmotic damage. Cytotoxicity via this mechanism is known as complement-mediated cytotoxicity (CDC). The Fc part of an

antibody can also bind to Fc γ receptors (Fc γ Rs) on NK cells and myeloid cells. Once the Fc γ R binds to the Fc part of the antibody, the effector cell releases cytokines and the contents of cytotoxic granules (perforin and granzymes) resulting in cell death by triggering of apoptosis (antibody-dependent cell-mediated cytotoxicity [ADCC]). The extent to which CDC and ADCC take place depends on the density of bound antibodies, and the class and subclass of the antibodies [2].

While alloantibodies can thus be detrimental for the renal allograft, the general efficacy of antibodies to bind their target has fuelled the interest in the use of antibodies for therapeutic purposes. Because immunoglobulins cannot pass the cell membrane, all targets are either found on the cell surface or are noncellular targets (e.g., complement factors). Given the central role that T cells play in the alloimmune response, it is not surprising that most efforts to control this response with antibodies have been directed toward the development of various kinds of anti-T-cell antibodies. More recently, antibodies against B cells and soluble molecules have gained interest for use in transplantation.

In the next paragraph, we will start with a brief overview of the use of antibodies in renal transplantation. Subsequently, the various monoclonal antibodies that are used in renal transplantation are described in more detail (see TABLE 1 for an overview of currently used monoclonal antibodies). Finally, new developments and future perspective will be addressed.

Intervention in the alloimmune response with antibodies

In 1899, Metchnikoff was the first to use rabbit immune serum to remove leukocytes from human blood. More than 60 years later, the first use of rabbit antiserum to prevent allograft rejection in renal transplant recipients was reported. Nowadays, polyclonal rabbit antithymocyte globulin (ATG; Genzyme, Cambridge,

MA, USA) is still commonly used to prevent and treat allograft rejection. Although highly effective, the use of these polyclonal antibodies is associated with several problems. Owing to the broad number of cellular targets, treatment is associated with considerable toxicity (mainly leukocytopenia and thrombocytopenia). Moreover, the formation of antirabbit antibodies diminishes the clinical effect after extended use and can also lead to adverse reactions such as serum sickness. Finally, the biological activity may vary between different batches of polyclonal antibodies.

Where polyclonal antibodies target a broad range of molecules, monoclonal antibodies have a single molecular target. Monoclonal antibody production starts with fusing B cells from immunized hosts with immortalized myeloma cells, thereby creating so-called hybridomas. After selecting the hybridomas that produce the desired antibody, these hybridomas are cloned and the monoclonal antibody is harvested from the supernatant. Usage of monoclonal antibodies provides the ability to specifically target cells or molecules involved in the alloimmune response. A rational strategy to achieve selective immunosuppression would be to target antigens that are expressed on lymphocytes that respond to alloantigens, but are absent on resting lymphocytes. The classical example of such a target is the α -chain of the receptor for IL-2 (CD25) [3]. As outlined later, anti-CD25 antibodies have an important place in current treatment regimens after renal transplantation. While the prototypes of monoclonal antibodies were mostly of mouse origin and elicited human antimouse immunoglobulin antibodies, the currently used chimeric and humanized antibodies are far less immunogenic (Box 1).

Anti-T-cell monoclonal antibodies are especially used for treatment of acute rejection and as induction therapy during the first days or weeks after transplantation. Induction therapy can have several goals that are not mutually

Box 1. Naming of monoclonal antibodies.

The naming of (new) monoclonal antibodies follows a strict pattern that has been described by the WHO in the International Nonproprietary Names (INN) Working Group Meeting on Nomenclature for Monoclonal Antibodies. The names of monoclonal antibodies are composed of a prefix, a substem A, a substem B and a suffix. The common suffix for monoclonal antibodies is 'mab'. Substem B indicates the species on which the immunoglobulin sequence of the monoclonal antibody is based. For example, 'a' for rat, 'xi' for chimeric, 'zu' for humanized and 'u' for human. Substem A indicates the target class (molecule, cell or organ), for example, 'c(i)' for cardiovascular, 't(u)' for tumor, and 'l(i)' for immunomodulating. Finally, the prefix can be random to contribute to a distinctive name. Therefore, basi-li-xi-mab, is a monoclonal antibody of chimeric origin, with an immunomodulating target. The only monoclonal antibody that does not comply with this naming is muromonab-CD3, which is short for murine monoclonal antibody against CD3.

Table 1. Monoclonal antibodies that are currently used in renal transplantation.

Name	Area of application	Origin	Target and mechanism of action	Dosing regimen	Main side effects
Alemtuzumab	Treatment of acute rejection Induction therapy	Rat, humanized	CD52 on mononuclear cells, depleting antibody	Single or double dose of 20–30 mg each iv. or sc. Pediatric dosing unknown	First-dose reaction after iv. administration, allergic reaction and increased incidence of infections
Basiliximab	Induction therapy	Mouse, chimeric	CD25 on T cells, nondepleting antibody	Two doses of 20 mg iv., 4 days apart. Pediatric dosing two doses of 10 mg	None
Rituximab	Blood group ABO-incompatible transplantation Desensitization Treatment of acute rejection Induction therapy	Mouse, chimeric	CD20 on B cells, depleting antibody	Single dose of 375 mg/m ² or two doses of 1000 mg, 2 weeks apart. Pediatric dosing 375 mg/m ²	Mild cytokine release syndrome, allergic reaction, neutropenia
Eculizumab	Treatment and prevention of antibody-mediated acute rejection Treatment of post-transplant hemolytic uremic syndrome	Mouse, humanized	Complement C5, blocks formation of membrane attack complex	Variable; loading dose of 1200 mg and weekly doses of 900 mg. Pediatric dosing unknown, Phase II trial underway [104]	Insufficient data; increased risk of infection with encapsulated bacteria

iv.: Intravenous; sc.: Subcutaneous.

exclusive: to prevent acute rejection, to induce tolerance, to minimize steroid use, or to postpone or reduce the treatment with calcineurin inhibitors, especially in cases where the risk of acute tubular necrosis is high. The anti-B-cell monoclonal antibody rituximab is used in ABO-incompatible transplantation, in desensitization protocols, and for treatment of antibody-mediated rejection. Moreover, it has an important place in the treatment of post-transplant lymphoproliferative disease. Currently, no monoclonal antibody is used or registered for maintenance immunosuppression.

Muromonab-CD3 (OKT3): mouse anti-CD3

The first monoclonal antibody approved for use in human renal transplantation was muromonab-CD3 (Orthoclone OKT3, Janssen-Cilag, Beerse, Belgium). It targets the CD3 protein on the surface of T cells, which is part of the T-cell receptor complex. Immediately after administration, CD3⁺ T cells are cleared from the circulation. In a prospective, randomized, multicenter trial, the efficacy in reversing acute rejection of renal transplants from deceased donors was clearly established. Not only did full-course treatment with OKT3 lead to superior reversal rates of acute rejection compared with high-dose steroids (94 vs 75%), it also showed efficacy in treating steroid-resistant rejections [4]. OKT3 has also been used as

induction therapy, although this is not based on randomized trials, and the drug has never been formally approved for this indication.

Unfortunately, OKT3 has numerous adverse effects. Especially the first administration can be followed by a cytokine release syndrome, which is caused by a transient activation of T cells, before they undergo cell lysis [5]. The clinical manifestations of this syndrome are fever, chills, headache, dyspnea, myalgia and hypotension. The release of cytokines probably also contributes to diarrhea, pulmonary edema, intra-allograft thrombosis, aseptic meningitis and temporary hearing loss. Furthermore, patients given OKT3 are more likely to develop serious infections (e.g., cytomegalovirus, Epstein–Barr virus, *Listeria* and *Mycobacterium*), and post-transplant lymphoproliferative disease [6]. For the treatment of acute rejection, OKT3 is outperformed by ATG, which is at least as effective and has a somewhat more favorable side-effect profile [7]. The declining usage of OKT3 has recently led to its removal from the market.

Alemtuzumab: humanized (rat) anti-CD52

CD52 is expressed on T cells, B cells, NK cells, monocytes, macrophages and dendritic cells. Early clinical trials with rat depleting anti-CD52 antibodies (Campath-1G and Campath-1M) as induction therapy in renal transplantation showed effective lymphocyte depletion with

reduced incidence of acute rejection, but with immunogenicity and also an increased incidence of infections [8]. The immunogenicity was reduced, but not completely eliminated, by humanizing the antibody (alemtuzumab; Campath-1H, Genzyme). The depletion of T cells caused by alemtuzumab is long lasting; T-cell levels recover to only 50% of baseline at 36 months after administration [9].

Alemtuzumab is indicated for the treatment of chronic lymphatic leukemia. Experience with the off-label use of alemtuzumab for treatment of acute rejection after renal transplantation is scarce and no randomized trials have been published on this subject. Most articles report on a few patients, merely demonstrating that allograft rejection can be reversed with alemtuzumab [10,11]. There is one larger trial describing 40 patients, in whom alemtuzumab was given because of steroid-resistant rejections, or rejections equal to or more severe than Banff 1B. Allograft survival was 74% after 1 year, with a patient survival of 95%. A total of 14 patients (35%) had infectious complications, of whom two patients (5%) died [12]. In another trial, 15 patients were treated with alemtuzumab for acute biopsy-proven rejection and compared with a historical control group of patients treated with methylprednisolone. All rejection episodes were reversed by alemtuzumab and 10-year allograft function was similar in both groups [13]. The use of alemtuzumab for the treatment of acute rejection may expand after the removal of OKT3 from the market.

Most experience with alemtuzumab stems from the use as induction therapy, especially in the setting of a reduced intensity of maintenance immunosuppression. In such a scenario, alemtuzumab might contribute to the induction of antigen-specific tolerance [14]. The use of alemtuzumab as add-on to standard triple or dual immunosuppression is considered to result in overimmunosuppression. In an initial trial with alemtuzumab induction therapy in 31 renal transplant recipients, a single dose of 30 mg was combined with low-dose cyclosporine maintenance immunosuppression. The incidence of early acute rejection episodes was approximately 20% and after 5 years of follow-up, there was no difference in incidence of rejection episodes, allograft function or allograft and patient survival, compared with patients who received cyclosporine, azathioprin and prednisolone [15]. Importantly, there were no differences in the incidence of malignancies or infections. Rejections in the alemtuzumab group tended

to occur beyond the first year after transplantation. Likewise, alemtuzumab induction followed by tacrolimus monotherapy resulted in similar graft and patient survival as tacrolimus in combination with mycophenolate mofetil and steroids [16]. In this trial, alemtuzumab-treated patients showed less acute rejections but an increased incidence of CMV infections. Multiple studies, mostly retrospective or observational in nature, have confirmed these results and underline the ability of induction therapy with alemtuzumab to reduce the intensity of maintenance immunosuppression [17,18]. However, in a pilot trial of 29 patients, the use of alemtuzumab with sirolimus monotherapy was associated with an increased risk of acute (humoral) rejection [19].

In several trials, alemtuzumab has been directly compared with other agents used for induction therapy, such as ATG or anti-CD25 antibodies. In general, the use of alemtuzumab was as least as effective as other induction agents in the prevention of acute rejection, while the number of drugs for maintenance immunosuppression could be reduced [20–23]. Although alemtuzumab causes profound depletion of T and B cells, the incidence of acute side effects is comparable with placebo. Commonly reported is an increased incidence of infections, although this is mainly observed in patients with a high overall burden of immunosuppression, either after transplantation or pretransplantation for the underlying renal disease.

Basiliximab: chimeric human-mouse anti-CD25

The first monoclonal antibodies targeting CD25 in humans were of mouse origin. Although effective in preventing acute rejection, the clinical applicability was limited by the development of antimouse immunoglobulin antibodies [24]. Basiliximab (Novartis Pharma, Basel, Switzerland) is a chimeric (human and mouse) nondepleting anti-IL-2 receptor antibody. In the first randomized, double-blind trial reported, 193 patients who received basiliximab were compared with 187 patients who received placebo [25]. Both groups received dual immunosuppressive therapy with cyclosporine and steroids. The incidence of biopsy-confirmed acute rejection within 6 months after transplantation was 30% in the basiliximab group, compared with 44% in the placebo group. The incidence of steroid-resistant first rejection episodes that required anti-T-cell antibody therapy was significantly lower in the basiliximab group (10 vs 23%). However,

the incidence of graft loss at 12 months post-transplantation was similar in both groups (12 vs 13%) [25]. Comparable results were found in another randomized, controlled trial 2 years later [26].

Patients treated with a triple immunosuppressive regimen, either azathioprin or mycophenolate mofetil added to cyclosporine and steroids, also benefit from induction therapy with basiliximab [27]. Basiliximab is generally associated with a tolerability profile that is similar to that reported with placebo.

Daclizumab: humanized (mouse) anti-CD25

Daclizumab (Roche, Basel, Switzerland) is a humanized anti-IL-2 receptor antibody. The efficacy of daclizumab in preventing acute rejection after renal transplantation was analyzed in two multicenter, randomized, placebo-controlled trials, in which maintenance immunosuppression consisted of triple and dual therapy, respectively. In both studies, a significant decrease in the incidence of biopsy-confirmed acute rejection was observed, without an increase in side effects [28,29].

Similarities & differences between basiliximab & daclizumab

In 2003, a meta-analysis of trials comparing basiliximab or daclizumab with placebo as induction therapy confirmed that the incidence of biopsy-proven acute rejection at 6 months is reduced by approximately 50% (95% CI: 37–58%) with a similar effect size for basiliximab and daclizumab [30]. All studies included in this meta-analysis used a cyclosporine-based maintenance regimen. By now, most immunosuppressive regimens are based on tacrolimus, which appears to be a somewhat stronger immunosuppressant than cyclosporine [31]. The number of clinical trials studying the effects of IL-2 receptor antagonists when added to a tacrolimus-based regimen is very limited and results from these studies are conflicting. In one trial, the addition of a single dose of daclizumab to tacrolimus, mycophenolate mofetil and steroids, seemed to reduce the incidence of acute biopsy-proven rejection during the first 6 months after transplantation compared with placebo (6 vs 16%) [32]. In pediatric recipients, the addition of basiliximab to a tacrolimus-based regimen had no benefits [33]. In a recent meta-analysis of the effects of IL-2 receptor antagonists by the Cochrane Renal Group, three tacrolimus-based and 26 cyclosporine-based regimens were included. Although combined analysis still confirmed

the reduction of the incidence of acute rejection within 1 year after transplantation compared with placebo (relative risk: 0.72; 95% CI: 0.64–0.81), the effect was not significant in the subanalysis of the three tacrolimus-based studies (relative risk: 0.66; 95% CI: 0.28–1.57) [34].

Next to the reduced incidence of acute rejection within 1 year after transplantation, this meta-analysis showed significant reductions in graft loss, CMV disease, early malignancies and transplant dysfunction, although these differences were not sustained more than 1 year after transplantation.

Studies with IL-2 receptor antibodies have mostly been performed in low-immunological-risk patients, and some studies report that in high-risk patients, ATG might be superior to IL-2 receptor antibodies for the prophylaxis of acute rejection [35–37], although the Cochrane meta-analysis does not support this conclusion. In low-immunological-risk patients, the use of IL-2 receptor antagonists enables the avoidance of steroids in patients treated with tacrolimus and mycophenolate mofetil [38,39].

In theory, targeting of the IL-2 receptor could also affect regulatory T cells with a CD4⁺CD25⁺FoxP3⁺ phenotype, which might impede graft acceptance. Although a shift of regulatory T cells from the CD25⁺ to the CD25[−] compartment during treatment with IL-2 receptor antagonists has been observed [40], several studies have demonstrated that the suppressive function of the regulatory T cells was maintained [41,42].

Based on the data summarized above, induction therapy with IL-2 receptor antagonists is recommended in the 2009 Kidney Disease: Improving Global Outcome (KDIGO) clinical practice guideline for the care of kidney transplant recipients [43]. The last published survey of the Organ Procurement and Transplantation Network (OPTN) in the USA reported that in 2006 approximately 28% of renal transplantations were performed with IL-2 receptor antagonist induction therapy [44]. It is likely that the KDIGO recommendations will cause an increase in this percentage in the future.

The only differences between basiliximab and daclizumab are in dosing and length of therapy. In clinical trials, up to 20% of patients did not receive the scheduled five doses of daclizumab, but it has been shown that two doses of daclizumab can provide prolonged blockade of the IL-2 receptor [45]. The similar efficacy of basiliximab and daclizumab, combined with the lack of approval for a limited dosing regimen of daclizumab, probably contributed to the voluntary withdrawal of daclizumab from the market in 2009.

Rituximab: chimeric human–mouse anti-CD20

Rituximab (Roche) is a chimeric human–mouse antibody against the CD20 molecule on B cells. After binding, it leads to clearance of B cells from the circulation. Rituximab is approved for the treatment of B-cell non-Hodgkin's lymphomas and severe rheumatoid arthritis.

In renal transplantation, the off-label use of rituximab is part of the recipient treatment when an ABO-incompatible living donor donates a kidney. These transplantations were previously only performed with intensive immunosuppression, plasmapheresis to remove anti-A/anti-B antibodies, and splenectomy. In 2001, the group of Tydén in Sweden replaced plasmapheresis with specific immune absorption of anti-A and/or anti-B antibodies, and splenectomy with a single dose of rituximab [46]. The initial experience with this regimen in 15 patients showed an incidence of acute rejection after 2 years of only 6.7%. Patient and graft survival were 100 and 86%, respectively. Moreover, cytokine release syndrome was not described and the incidence of infections or malignancies was not increased [47]. The favorable results of similar protocols have been confirmed by others, and have led to a substantial rise in the number of ABO-incompatible living donor renal transplantations [48].

Patients with a high level of anti-HLA antibodies or with a positive cross-match wait long, and sometimes in vain, for a kidney. To reduce the level of anti-HLA antibodies, 76 selected patients received rituximab and intravenous immunoglobulin before transplantation [49,50]. Although the incidence of acute rejection after transplantation was relatively high (37%), the biggest potential gain of this approach is the possibility to transplant patients, who otherwise would have continued dialysis treatment.

In steroid-resistant rejections, clusters of B cells can be found in the renal interstitium, which are possibly associated with worse graft survival [51,52]. Although most reports involve selected patient groups, acute or chronic antibody-mediated rejection or steroid-resistant rejection episodes can respond to rituximab (even when there was no response to ATG and/or plasmapheresis) with clusters of B cells successfully being removed from the interstitium [53–56].

The data on the use of rituximab as induction therapy are limited. Based on their favorable experience with rituximab in ABO-incompatible transplantations, Tydén *et al.* evaluated the effectiveness and safety of single-dose rituximab induction therapy compared with placebo, added

to tacrolimus-based triple therapy. The incidence of acute rejections after 6 months was 12% in the rituximab group and 18% in the placebo group, which was not significantly different [57]. Another trial, using two doses of rituximab with steroid-free maintenance immunosuppression, was halted early due to an excess rate of acute cellular rejection. This raises the possibility that regulatory B cells may be depleted by rituximab [58]. We are currently performing a randomized controlled trial with a similar design to that of Tydén *et al.* in a larger group of patients [101].

Rituximab has also successfully been used in the treatment of recurrent focal segmental glomerulosclerosis and membranous nephropathy after renal transplantation. However, controlled studies for these indications are lacking and in many of the reported cases the efficacy of rituximab is difficult to assess since it was combined with other immunosuppressive drugs or with plasmapheresis [59]. Finally, rituximab has an important place in the treatment of post-transplant lymphoproliferative disorder [60].

Administration of rituximab can be followed by a mild cytokine release syndrome. Although rituximab induces long-lasting B-cell depletion, the risk of infections appears to be limited [47,61,62]. Several cases of late-onset neutropenia have been described [63].

Eculizumab: humanized (mouse) anti-C5

Eculizumab (Alexion, Cheshire, CT, USA) is a humanized (human–mouse) monoclonal antibody directed against the complement protein C5. It blocks the cleavage of C5 and halts the formation of the membrane attack complex. It is successfully used in paroxysmal nocturnal hemoglobinuria [64]. Eculizumab could potentially be beneficial in renal transplantation for treatment or prevention of antibody-mediated rejection, which is accompanied by activation of the complement system. The first case reports show that eculizumab can be safely and effectively used in selected patients to prevent injury from CDC [65]. This creates a window of opportunity for other therapies to clear the donor-specific antibodies. After renal transplantation, hemolytic uremic syndrome (HUS) may occur either as a recurrent or *de novo* form. During recent years, it has become clear that dysregulation of the complement alternative pathway leading to continuous complement activation is involved in the pathogenesis of HUS [66]. Several case reports have now demonstrated that treatment with eculizumab can improve outcome in patients with HUS after

renal transplantation [67,68]. Since eculizumab diminishes the defense against encapsulated bacteria, especially meningococci, patients should ideally undergo meningococcal vaccination prior to receiving the first eculizumab treatment. The response to this vaccination could however be suboptimal, especially during (intensified) immunosuppressive therapy.

Future perspective

Challenges in transplantation that are not yet met are long-term toxicities associated with current regimens, and immune targets that are not affected by the current drugs. Ultimately, the induction of donor-specific tolerance remains the holy grail. The development of new monoclonal antibody therapies to address these issues, have been hampered during the last couple of years. The monoclonal antibody efalizumab against leukocyte function-associated antigen-1 (a molecule found on all T cells and B cells and important in cell adhesion, migration and interaction) has been proven to be effective in psoriasis and was investigated in a Phase I/II trial in renal transplantation [69]. However, it has been withdrawn from the market because of the association with progressive multifocal leukoencephalopathy [70]. Several monoclonal antibodies against costimulatory molecules such as CD40 and CD154 have been developed and appeared promising in experimental models. One of these, the anti-CD154 antibody toralizumab has been used in clinical trials in autoimmune diseases, but the occurrence of thromboembolic complications with this and other anti-CD40 ligand antibodies halted further studies [71]. Currently, only very few clinical trials with new monoclonal antibodies in renal transplantation (e.g., a Phase I/II trial on the anti-T-cell receptor antibody TOL101 [102]) are registered in public trial registries.

In the next years, we can therefore expect the off-label use of monoclonal antibodies that have originally been developed for other indications. Examples include epratuzumab, a humanized anti-CD22 antibody targeting B cells; belimumab, a human anti-BLyS (B-cell-stimulating factor) antibody approved for the treatment of systemic lupus erythematosus and now under investigation for desensitization of renal transplant candidates [103]; and tocilizumab, a humanized antibody against the IL-6 receptor, registered for treatment of rheumatoid arthritis. Although IL-6 is massively released during reperfusion of a renal allograft, blocking of the IL-6 receptor has produced conflicting results with respect to the prevention of ischemia–reperfusion injury [72,73].

A next step that might change the face of transplantation is the development of (combinations of) monoclonal antibodies for maintenance therapy, in an attempt to improve the specificity of long-term immunosuppression without the requirement for, and toxicity of, daily oral agents (especially calcineurin inhibitors and steroids) [74]. Maintenance immunosuppression with monoclonal antibodies has (at least in theory) become possible, largely through the perfection of protein humanization and thereby virtual elimination of long-term immunogenicity [75].

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Executive summary

Intervention in the alloimmune response with antibodies

- The technique of monoclonal antibody production provides the ability to target specific cells or molecules involved in the alloimmune response.

Muromonab-CD3 (OKT3): mouse anti-CD3 (currently no longer available)

- Treatment of acute renal allograft rejection with the T-cell-depleting OKT3 led to superior reversal rates compared with high-dose steroids, but was associated with severe side effects.
- For the treatment of acute rejection, OKT3 is outperformed by the polyclonal ATG, which is at least as effective and has a somewhat more favorable side-effect profile.

Alemtuzumab: humanized (rat) anti-CD52

- Small studies suggest that treatment with alemtuzumab can reverse steroid-resistant acute rejection.
- A single dose of alemtuzumab given as induction therapy allows to reduce the intensity of maintenance immunosuppression, probably without negative effects on rejection incidence or graft survival.
- No acute side effects of treatment with alemtuzumab are reported, but in the long term there is an increased incidence of infections.

Executive summary

Basiliximab (chimeric human–mouse anti-CD25) & daclizumab (humanized [mouse]) anti-CD25 (currently no longer available)

- Randomized, placebo-controlled clinical trials demonstrated that adding basiliximab or daclizumab to a cyclosporine-based regimen reduces the incidence of acute biopsy-proven rejection at 6 months by approximately 50%. With either basiliximab or daclizumab induction therapy, minimization or withdrawal of steroids can be safely performed.
- Despite the significant drop in incidence of acute rejection, improvements in long-term graft survival have not been demonstrated with either basiliximab or daclizumab induction therapy.
- Administration of basiliximab or daclizumab is devoid of acute side effects and does not appear to increase the incidence of infection or malignancies.
- Data on the added effect of basiliximab or daclizumab to a tacrolimus-based regimen are limited and conflicting.

Rituximab: chimeric human–mouse anti-CD20

- In blood group ABO-incompatible transplantation, rituximab is part of the regimen of intensive immunosuppression and is associated with a low incidence of rejection.
- Patients with a positive cross-match or high levels of anti-HLA antibodies can be successfully transplanted after desensitization with rituximab and intravenous immunoglobulin.
- Rituximab can reverse acute allograft rejection, even after high-dose steroids or anti-T-cell therapies have failed.
- Rituximab plays an important role in the treatment of post-transplant proliferative disease.
- Recurrences of focal segmental glomerulosclerosis and membranous nephropathy after renal transplantation have successfully been treated with rituximab.
- Rituximab has not been associated with an increased incidence of infections or malignancies.

Eculizumab: humanized (mouse) anti-C5

- The first case reports suggest that eculizumab can be safely and effectively used as rescue therapy in antibody-mediated rejections and in post-transplant hemolytic uremic syndrome.

Future perspective

- The development of monoclonal antibodies against other relevant targets in the alloimmune response (e.g., CD154 and LFA-1) has been hampered by safety problems.
- Monoclonal antibodies developed in other areas (e.g., anti-IL-6 receptor antibodies) may be useful in renal transplantation.

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