Pathophysiology and treatment options of chronic renal allograft damage

Uwe Heemann¹ and Jens Lutz²

Correspondence and offprint requests to: Uwe Heemann; E-mail: uwe.heemann@lrz.tum.de

ABSTRACT

Chronic rejection is a poorly understood entity albeit a frequent cause of graft failure. Despite the advent of new immunosuppressive agents, neither the slope of graft destruction nor the frequency is ameliorated. There are a number of hypothesis which try to explain the conundrum of chronic graft destruction: ongoing rejection, antibody-mediated rejection, poor choice of organs, hyperfiltration, calcineurin inhibitors (CNI) nephrotoxicity and non-compliance among them. None of these hypotheses can explain all features of the process, thus, it is likely that they act in combination. What seems to be clear is a beneficial effect of early angiotensin-converting enzyme (ACE)/AT1 blocker treatment. It is less clear, however, whether a reduction or a switch from CNIs to other immunosuppressants prolongs graft survival. This review highlights the pathophysiological aspects that are important for the development of chronic allograft damage in the context of possible treatment options.

PATHOPHYSIOLOGY OF CHRONIC ALLOGRAFT DAMAGE

Despite major improvements in the care of patients after kidney transplantation, one of the major problems during the long-term follow-up of these patients is chronic allograft damage. However, this is a difficult term as it is often mixed with terms such as chronic rejection that comprise only some parts of the complex pathogenesis of this entity. In the complex pathogenesis of chronic allograft damage, which is only partly understood today, alloantigen-dependent and -independent factors act together to initiate inflammatory reactions that eventually lead to tissue damage with a loss of nephrons in the graft followed by fibrosis and tubular atrophy (TA). This leads to graft dysfunction and eventually graft failure.

When successful kidney transplantation programmes started in the mid-1950s of the last century, the major problem was graft loss within the first days after transplantation. The focus

1Department of Nephrology, Klinikum rechts der Isar, München, Germany and
2Department of Nephrology, Universitätsklinikum Mainz, Mainz, Germany

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was rather to discriminate rejections mediated through antibodies in a hyperacute, mainly complement-driven, fashion within minutes after transplantation from rejections mediated by preformed antibodies within the first days after transplantation as well as T-cell-mediated rejections during the first weeks. Thus, long-term performance of the grafts was not the main focus of the clinicians at this time. It was assumed that once this first period was overcome, the graft would basically last as long as the recipient prevailed. The only problems seemed to be tumours and infections related to the immunosuppressive therapy necessary for transplantation.

Once it was clear that grafts were lost even after years following transplantation and were not related to malignancies or infections, the term chronic rejection was coined [1, 2].

Until the beginning of the 1990s, it was the general perception that this long-term graft destruction was due to the development of antibodies against donor-derived alloantigens slowly destroying the graft. Thus, alloantigen-dependent pathogenic factors were thought to be the main obstacle for successful long-term allograft function.

During the following years, however, a number of groups analysed chronic rejections and questioned the antibody hypothesis [3]. With the advent of animal models, albeit in rats, came the notion that antibodies were not needed to destroy a graft in the long term [4]. Thus, alloantibody-independent pathogenic factors came into the focus of interest.

This was highlighted by observations of the first transplantations between twins by Murray and colleagues [5] in the 1950s. The kidneys were lost over the long term and the biopsies revealed a histopathology which would nowadays be described as interstitial fibrosis (IF)/TA [6, 7]. Thus, even without any long-term immunosuppressive therapy and most likely without major differences in HLA, kidneys were lost due to chronic graft damage. Even today, kidneys transplanted from one genetically identical twin to the other do not last forever, although no immunosuppressive treatment was used for most of the time with no rejections detectable [8].

When chronic graft damage was in the focus of animal research for the first time in the 1990s, it became evident that almost all features attributed to chronic allograft damage in man also developed in uni-nephrectomized rats, albeit after a very long time; however, none of these rats died from kidney failure [9]. Even in old non-nephrectomized rats, the histological features of the kidneys were similar to those of chronic allograft damage.

In humans, we know that kidney function deteriorates with age. In old kidneys, we can also find changes typical of chronic allograft damage [10]. However, in most cases, there are a lot of other changes apparent, such as atherosclerosis or features commonly attributed to hypertension or infections.

In the light of the evidence for different alloantigen-dependent and -independent factors, particularly antibody-mediated allograft rejection, contributing to chronic graft damage, the histopathological BANFF classification has been revised, now differentiating chronic T-cell-mediated rejections, chronic antibody-mediated rejections and chronic changes without evidence of other aetiologies (IF/TA) [11].

Alloantigen-independent factors such as age, gender, weight, metabolic derangements, arterial hypertension, infections, calcineurin inhibitor cytotoxicity, genetic factors, brain death of the donor or ischaemia/reperfusion (I/R) injury together with alloantigen-dependent factors such as rejections, HLA mismatch or donor-specific antibodies can influence the development of chronic graft damage [12].

How could the mentioned pathogenic factors induce chronic allograft damage?

**Initial damaging insults on the graft**

An initial damaging insult on the graft tissue is mediated through I/R or even before transplantation through the cytokine release during the development of brain death [13]. This could cause an acute inflammation that further develops into chronic inflammatory processes eventually leading to chronic graft damage with graft dysfunction or even a complete loss of function [14]. Furthermore, the disease or trauma responsible for the death of the donor could have also induced graft damage either directly or through a period of poor perfusion or oxygenation, respectively, that could translate into acute/chronic inflammatory processes within the graft after transplantation. For all these entities, a vast amount of data correlating these with graft survival exists [13, 15].

I/R injury as a consequence of the organ transfer from the donor to the recipient is of special importance as it can directly initiate graft damage by apoptosis/necrosis of renal cells and inflammatory reactions [16]. In rat experiments, both I/R and mere surgery were proven to cause damage to the grafted organ, resulting in a reduced graft survival [17]. I/R injury has also been shown to result in progressive fibrosis of renal tissue and could be a link between alloantigen-independent damage and alloantigen-dependent graft damage, thus, contributing to graft damage also by the initiation of graft rejections [18]. Renal cells, particularly, tubular and endothelial cells become activated after I/R and express MHC class II molecules after I/R [19], which make them more susceptible for alloantigen recognition and, thus, T-cell activation. Furthermore, molecules such as decay-accelerating factor (DAF), which protect cells from antibody binding, cannot be produced any longer [20]. Thus, cells are prone not only to recognition by T-cells but also to antibody-mediated damage.

I/R injury is the result of a number of events. The first event is the I/R due to transplantation itself. However, as was mentioned before, the kidney mass transplanted does not equal the mass of one healthy kidney, but is reduced depending on age, body weight, cause of death and gender of the donor as well as tissue damage in the wake of I/R and surgery.

Taken together, the workload on the remaining nephrons is increased and angiogenic hormones are produced. To initiate this production, a certain level of hypoxia is needed. This induces the production of vessels to facilitate the transport of enough oxygen to the tubular system. Once a sufficient number of vessels have been formed, the blood supply may be enough for the work needed and no further relative ischaemia will occur.
This is a period of calmness within the graft. However, every infection or a very high uptake of proteins will stimulate ischaemia anew. At a certain level, the supply of oxygen will not be sufficient any longer for the tubular cells, at which stage a permanent activation of the system will be present. This induces a vicious cycle of tubular activation, glomerular sclerosis and alloantigen presentation, inflammation and TA/IF, which is the most likely order of events to cause chronic allograft damage.

Following episodes of infection, mostly MHC class II molecules are expressed while DAF-like molecules are still produced [21]. Under these circumstances, a T-cell-mediated rejection is likely to occur.

However, in isografts, albeit evident, this damage was not sufficient to significantly reduce the lifespan of the grafts. Thus, it cannot be only the effect of I/R on the graft tissue.

Could the nephron mass influence the development and the velocity of progression of chronic graft damage?

**Reduced nephron mass**

Interestingly, in an animal model of kidney transplantation, nephron mass reduction and kidney and animal survival were significantly reduced [22]. Differences in nephron mass of the graft in relation to the requirements of the recipient could also explain differences in graft outcome with respect to gender or donor/recipient age.

The speed of chronic graft damage is somewhat similar to a 5/6 nephrectomy. One explanation may be the long-term consequences of episodes of acute rejection with the initiation of chronic, also alloantigen-independent, inflammatory processes. However, this falls short, as in all retrospective as well as in prospective studies, the actual glomerular filtration rate (GFR) predicts long-term survival, and, even under optimal circumstances, this calculated survival is shorter than that of a living donor. Of course, this difference may be due to the fact that a living donor is healthy while there is always a disease-causing kidney failure. On the other hand, one would expect that this disease shortens the life expectancy of the recipient rather than that of the graft.

Thus, we have to look for other explanations.

**T-cell- and antibody-mediated insults**

Apart from alloantigen-independent factors, also alloantigen-dependent factors, such as the frequency of cellular/humoral rejection episodes, the number of HLA mismatches or the presence of donor-specific antibodies determine the development of chronic allograft damage and, thus, long-term graft performance.

T-cell-mediated rejections have been shown to contribute to the chronic graft damage [23–25]. However, it is not entirely clear today how findings in protocol biopsies resembling T-cell-mediated rejection without evidence of deteriorating graft function or vice versa should be interpreted. Indeed, the results of protocol biopsies may very well be a snapshot probably indicating ongoing processes that do not require immediate therapeutic actions [26]. Further analysis of protocol biopsies should answer these questions.

Antibody-mediated rejection, on the other hand, is considered to be a major force behind chronic graft deterioration. Again from protocol biopsy programmes, we have learnt that the presence of donor-specific antibodies and the detection of C4d in the graft tissue are correlated with reduced graft survival. Furthermore, the detection of donor-specific antibodies before transplantation is also correlated with poor graft outcome, while renal cells are also more perceptive to antibody-mediated destruction after ischaemia [27]. Thus, we may assume that some alloantibodies can cause harm to the graft.

This is obviously true for vascular or accelerated forms of rejection where antibodies are the primary cause of almost immediate graft destruction [28, 29]. However, antibody binding must not necessarily be harmful for the graft tissue. From experiments in xenotransplantation, we learnt that once the first period after transplantation is over the mere presence of antibodies against donor antigens does not predict graft outcome [30, 31]. Antibody binding was detected in the graft which had even protective effects, which was named accommodation. While a positive B-cell cross-match is correlated with poor long-term graft survival, this effect may result from early rejection episodes. Even in living donation where the initial cross-match between a donor and a recipient was positive, when the antibodies had been removed and the first period was over, there was no evidence of an ongoing graft destruction even in the presence of donor-specific antibodies. In some cases, the cross-match turned positive and there was still no sign of rejection [32].

Last but not least, in AB0-incompatible transplantation, basically all grafts stain positive for C4d without any other sign of rejection and these grafts seem to last even longer than standard living grafts [33, 34]. However, antibodies against isoagglutinins may have properties different from HLA-specific ones and the recipients may be better monitored than the standard recipient. Altogether, we do not know under which circumstances alloantibodies are harmful or protective (i.e. in accommodation). However, it is clear that alloantigen-dependent pathogenic factors play an important role in chronic graft damage as also in liver transplantation the number of recipients that do not need immunosuppression after a prolonged period is small. Even longer times after transplantation, mechanisms such as CMV, polyoma BK virus or bacterial infections as well as non-compliance or withdrawal of immunosuppression exist that trigger rejection episodes and lead to the generation of alloantibodies [35, 36].

Therefore, a possible explanation for chronic alloantigen-dependent graft damage would be a series of rejection episodes.

**Drug toxicity**

However, although repetitive rejections have been observed, they did not have apparent consequences in most cases [37]. Furthermore, if repetitive acute rejection episodes would be the major reason for chronic rejection, more immunosuppression should help to cope with the problem. Here, the side effects of CNIs were accused of causing chronic allograft damage [38]. In some studies, basically all changes in
the grafts were attributed to CNIs. At present, it cannot be distinguished between direct toxic effects of the drugs and indirect effects such as hypertension or diabetes. However, in animal models, the changes appear even without the presence of CNIs or any other drugs. In humans, graft loss is associated with the absence of immunosuppression and, thus, even if CNIs might be harmful for the graft in the long term due to their toxicity, they are also important for graft survival due to their immunosuppressive effects. Interestingly, it has been observed that patients with CNI toxicity had a better graft survival compared with patients without signs of CNI toxicity [39]. Furthermore, even before the advent of CNIs, chronic graft damage was apparent in human graft recipients [40]. Altogether, the role for CNIs in the development of chronic graft damage is not entirely clear, although some patients exist who have substantial CNI toxicity with the respective consequences regarding chronic graft damage.

**Infections**

As mentioned above, infections can induce rejection reactions, thus, contributing to chronic graft damage. However, they can also independently induce graft damage. Here, repetitive urinary tract infections also with an accompanying pyelonephritis of the graft may be harmful to long-term graft function [41, 42]. It has been demonstrated that CMV infections can contribute to chronic graft damage through direct damaging effects on the graft tissue following CMV infection or through the triggering of graft rejection [40]. On the other hand, BK Polyoma virus infection can also result in chronic graft damage [41, 43]. Here, a direct reactivation in the graft's urothel can initiate the infection, which can then directly damage the graft or initiate rejections of the graft. The exact mechanism of viral reactivation is not entirely clear but risk factors include, among others, immunosuppression with tacrolimus/mycophenolate mofetil (MMF) or male gender [44].

**Recurrent and de novo glomerular disease**

Basically, the recurrence of glomerulonephritis or the de novo development of glomerulonephritis can also contribute to graft damage. Particularly, the recurrence of focal segmental glomerulosclerosis reduces graft half-life, while other forms of recurrent glomerulonephritis have only minor or even no significant effect on graft survival [45]. Furthermore, chronic damage to the graft could also be enhanced due to diabetes mellitus or arterial hypertension, particularly in patients with a rather poor therapeutic control of these conditions.

**Proteinuria**

What are the consequences of chronic insults related to alloantigen-dependent and -independent pathogenic factors to the graft tissue? A critical function of the kidney is glomerular filtration. As soon as a glomerulus is completely obliterated, the related tubular apparatus will be destroyed and other nephrons have to compensate for the missing function of the destroyed nephron. As a result of the declining number of nephrons, the intraglomerular pressure in the remaining functioning glomeruli is enhanced, resulting in an increasing proteinuria. The tubular cells of this nephron markedly enlarge to recover these proteins [46]. However, the fewer glomeruli that are available, the more enlarged the tubular system, and the more pressure and blood flow is needed to supply the tubuli with oxygen. At a certain point, the tubular system is not able to recover all proteins in the urine anymore. At this point, proteinuria becomes overt, causing inflammatory processes in the glomeruli and the interstitium, promoting glomerulosclerosis, IF and TA. This correlation between chronic graft damage and proteinuria was first described in rats and later in humans [47]. The significance of glomerular hyperfiltration for the decline of renal function was recently shown in a study in patients with diabetic nephropathy [48]. Thus, an important result of glomerular hyperfiltration contributing to the progressive loss of graft function is proteinuria. However, reasons other than glomerular hyperfiltration for the development of significant proteinuria in patients after renal transplantation must exist as patients with a single kidney (i.e. living related kidney graft donors) do not necessarily develop chronic overt proteinuria. In living donors as well as in animal experiments, the loss of one kidney has no major impact on overall survival [49]. Here, chronic antibody-mediated rejections could play an important role for the development of proteinuria. An association exists between the presence of donor-specific antibodies/antibody-mediated chronic rejection and the damage of the basal membrane, which is histologically characterized by double layering of the glomerular basal membrane [50–52].

Proteinuria initiates a vicious circle with the destruction of nephrons leading to an increase in hyperfiltration and further destruction of glomeruli and nephrons eventually leading to the destruction of the kidney graft with IF, TA and glomerulosclerosis with graft failure. Furthermore, proteinuria could also contribute to the initiation of rejection processes in the graft. Here, antigen presentation via dendritic cells in the kidney could play an important role. From a number of experiments, particularly in mice, we learnt that dendritic cells are core to the development of nephrotoxic glomerulonephritis [53]. Dendritic cells are located around the tubular cells and process all antigens present in the interstitium. In severe proteinuria, antigens enter the interstitium, which are not present in the normal urine as they are too small to pass the glomerular basement membrane. Once the glomerular basal membrane is damaged, however, macromolecules enter the urine, are back-filtered and presented in the interstitium. These antigens together with additional alloantigens may activate dendritic cells and in the following cascade of events may trigger a rejection [54].

The question is whether initial insults or whether continuously repeating insults lead to a process of chronic inflammation related to the mentioned pathogenic factors that eventually result in chronic allograft damage. The concept that an initial insult leads to further graft damage is demonstrated in an experimental model of chronic graft damage analysing the inhibition of metalloproteinases (MPs) [55]. Here, an inhibition of metalloproteases during the immediate period after transplantation reduced chronic graft damage significantly while an inhibition of MPs at a later time point
increased chronic graft damage. However, in the development of chronic allograft damage, a combination of initial insults together with continuously repeating (i.e. acute rejections, infections) or lasting insults (i.e. donor-specific antibody) will lead to chronic graft damage [55].

Altogether, a combination of alloantigen-dependent and -independent factors on the basis of a reduced nephron mass together with the failure of protection against antibodies results in chronic allograft damage.

**Therapeutic options**

In animal experiments, all of the features associated with chronic allograft damage including TA, IF, intimal thickening of vessel walls and glomerular sclerosis have been ameliorated by drugs or other interventions [56, 57]. However, in all experiments, prevention was easier and more effective than treatment. Furthermore, the later the initiation of the intervention, the less pronounced was its effect.

**Donor treatment**

As I/R damage seems to be an important initial event for chronic allograft damage, it would be an important goal to reduce it in order to improve the long-term graft performance. Thus, prevention starts with interventions even before the removal of the graft from the donor, particularly in cadaveric organs. Under these circumstances, dopamine seems to have a remarkable effect on long-term allograft survival in humans and animals [58]. It is assumed that this effect relates to ameliorated I/R damage.

**Organ storage/machine perfusion**

Once the organ is removed, major efforts have been undertaken to ameliorate the damage due to ischaemic storage, surgical trauma or reperfusion injury, using improved storage solutions, machine perfusion during cold storage or drugs reducing the effects of reactive oxygen species.

While the effects of storage solutions have been confirmed in a number of trials [59–61], the effects of machine perfusion remain unclear despite a large randomized trial [62]. However, key to successful transplantation and an optimal long-term graft performance is a perfect operation technique. This was shown in experimental models with very short ischaemia times and a perfect anastomosis of the ureter. In such models, graft damage progressed extremely slowly, although immunosuppression was stopped. Evidence in the situation of clinical transplantation comes from living related transplantation with short ischaemia times where graft half-lives are significantly longer when compared with cadaveric kidney transplantation [63].

**Strategies to reduce adhesion of leucocytes**

As inflammation is a key feature after I/R damage, attempts have been made to reduce the inflammatory response by blocking the binding of leucocytes to the injured tissue, with antibodies directed against adhesion molecules (i.e. intercellular adhesion molecule 1) [64]. In animal experiments, antibodies which prevent the adhesion or infiltration of leucocytes also prolong graft life. However, the effects are much smaller than those of standard immunosuppressants, and it has to be mentioned that such effects are likely to affect long-term rather than short-term graft survival, and studies in humans published so far focused primarily on acute rejection and 6-month or 1-year results. Thus, with respect to the short-term observation periods, it is not surprising that most of these antibodies failed to demonstrate a significant impact on overall graft survival in humans so far.

**Renin–angiotensin–aldosteron system blockade**

Any intervention which reduces the number and particularly the severity of acute rejection episodes helps to prolong graft survival and, thus, reduces chronic graft damage. However, what strategy could be used once the first period after engraftment has passed? In animal experiments, cyclosporine or tacrolimus in low doses did not reduce graft survival. On the contrary, they correlated with a longer graft survival and a reduction of the features of chronic rejection [65]. An interesting question is whether these results are due to their immunosuppressive activities or due to the reduced GFR associated with calcineurin inhibitors, an effect which would mimic that of ACE inhibitor treatment, which has been shown to reduce the speed of graft destruction in animals [66]. Similar albeit less pronounced effects were observed with the lowering of blood pressure. Interestingly, experimental models demonstrated that blockade of the renin–angiotensin–aldosteron system (RAAS) by angiotensin (AT) receptor blockers is only effective with respect to the development of chronic graft failure if continuous treatment is started early after transplantation [67].

**Choice of immunosuppressive agents**

It is of interest that no randomized study analysed the optimal trough level of cyclosporine or tacrolimus long-term after transplantation so far. It is likely that such long-term trough levels are much lower than that necessary to reduce the number of rejection episodes immediately after transplantation. However, the realization of such studies is not easy as an interest in the prescription of lower drug doses from an economic point of view within the pharmaceutical industry does not exist. In retrospective observational studies, however, lower doses, particularly of tacrolimus, were associated with a better graft survival [68].

Intimal thickening of graft vessels was reduced in humans after the treatment with mammalian target of rapamycin (mTOR) inhibitors [69]. In animals, these substances were even able to improve graft function and ameliorated chronic graft damage [56]. In principle, mTOR inhibitors would be an interesting candidate for a combination therapy with RAAS blockers (i.e. renin inhibitors, ACE inhibitors and AT-antagonists) as the antiproliferative effects of both classes of substances could act together while the effect on GFR would be balanced as mTORs increase GFR after cessation of CNIs while RAAS blockers decrease GFR due to their haemodynamic effects. However, mTOR inhibitors are difficult to use in patients with impaired graft function (i.e. in the presence of chronic allograft damage), as their side effects (i.e. proteinuria, oedema and pneumonitis) increase while their
agreeability decreases [70], which altogether decreases their clinical applicability. So far, no trials to analyse the combination of mTOR inhibitors with RAAS blockers have been performed.

A further possibility to reduce chronic graft damage would be a treatment including mycophenolic acid, which is already a clinical routine. This drug proved to be effective in experimental models of chronic graft damage and in a retrospective analysis in humans [71]. Possible mechanisms of action are an interference with B-cells, thus, reducing B-cell/T-cell interaction and indirectly antibody production as well as matrix production in the interstitium [72–74]. All data available so far indicate, however, that the effect is less pronounced the later the treatment is initiated. As many patients already receive MMF after transplantation, only a small number of patients could be switched to MMF and, thus, would profit from these theoretical benefits.

As mentioned above, CNIs could contribute to chronic graft damage through the development of chronic CNI toxicity and indirectly promote alloantigen-independent pathogenic factors of chronic graft damage such as arterial hypertension and metabolic disorders (glucose and lipid metabolism), particularly in the standard combination with steroids. However, CNI-free immunosuppressive protocols using only MMF and steroids have been described but are associated with an increased number of acute rejections [75, 76]. It has to be demonstrated in the future how this affects long-term graft outcome.

Maintaining a certain level of immunosuppression seems to be important for a good long-term graft function. The co-stimulation signal blocker belatacept could be an option to avoid the side effects of CNIs while maintaining a certain amount of immunosuppression. It has successfully been used in clinical trials and was recently introduced into the market. However, also with belatacept, an increased number of acute rejections was observed. The potentially higher incidence of certain tumours or infections (post-transplant lymphoproliferative disorder, tuberculosis), respectively, warrants further investigation [77–79].

In recent years, the importance of donor-specific antibodies in the pathogenesis of chronic graft damage became clearer. Thus, the reduction or even inhibition of the production of DSAs would be an important target in order to reduce alloantibody-mediated chronic graft damage. Rituximab, which leads to a nearly complete elimination of B-cells, has been shown to be effective in acute antibody-mediated rejections [80]. However, in chronic antibody-mediated rejection, its therapeutic effects are not evident so far. This could be related to the fact that chronic graft damage related to alloantibodies proceeds very slowly in a subclinical manner. Thus, in an individual patient, it is not clear when this process was initiated and, thus, the time point of treatment might be too late in order to reverse the already present chronic changes of graft destruction. In order to better understand the progression of alloantibody-mediated graft damage, clinical studies on the basis of protocol biopsies could be valuable.

**Donor/recipient allocation**

Basically, it would be logically consistent to find the perfect donor for a certain recipient on an individual basis in order to reduce the development of chronic allograft damage. This is already the policy in most transplant programmes worldwide where factors such as HLA match/mismatch and ischaemia time are taken into account for organ allocation. However, as the age of the recipients and donors is increasing, programmes like the European Senior Programme [81] (‘Old-for-Old Programme’) have been initiated in order to allocate grafts from older donors to older recipients as life expectancy is shorter in older recipients and younger ones would receive organs from younger donors who would have also a larger nephron mass compared with older donors, thus meeting more the requirements of younger recipients in order to retard the development of chronic graft damage.

**Experimental or future approaches**

Other potential options to reduce the production or action of alloantibodies within the graft include the inhibition of B-cell proliferation by the BAFF inhibitor [82], the reduction of plasma cells by proteasome inhibitors [80, 83] and the reduction of the antibody effects by the inhibition of the complement cascade [84]. While bortezumib has been used in small observational patient series in acute antibody-mediated graft rejection, there are no observations so far in chronic antibody-mediated rejection. As mentioned above, chronic alloantibody-mediated rejection could progress slowly in a subclinical manner, which makes the initiation of studies aiming at chronic antibody-mediated rejection difficult as the time point to begin treatment is not clear and late initiation of treatment might be not effective any more.

Theoretically, it would also be possible to directly influence the process of fibrosis in the graft. Here, two potential therapeutic options, which have been proven successful in experimental models, have to be mentioned: the effects of sex hormones and the effects of MPs that are important for the process of interstitial matrix turnover. While oestrogens cause beneficial effects, testosterone promotes the process of chronic graft damage. Dihydroandrosterone (DHT), a derivative of progesterone and testosterone, is likely to play a key role in this respect [85]. The level of DHT is correlated with the level of fibrosis and interventions aimed to reduce DHT levels ameliorate IF [86]. As a second option, a timely limited inhibition of MPs during the immediate period after transplantation significantly ameliorated graft fibrosis [55]. Interestingly, a later MP inhibition remarkably increased chronic graft damage. This demonstrates that the time point of a specific intervention is crucial for its effects on chronic graft damage. However, as these findings are based on animal experiments, it is impossible to adapt them directly into a clinical situation and, moreover, it is not clear what effects an inhibition of DHT or MPs would have in humans.

Taken together, the treatment options mentioned so far have in common that they reduce the speed but not the progression of graft damage itself. Thus, the understanding of
the pathogenesis of chronic allograft damage has improved over the past, while the therapeutic options still remain scarce.

CONFLICT OF INTEREST STATEMENT

None declared.

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