Treatment Approach for CA T-Cell Mediated Kidney Rejection

Subjects: Transplantation

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Chronic active T-cell mediated kidney rejection (CA TCMR) refers to the term that was described for the very first time during the XIII Banff Conference on Allograft Pathology in 2015 as a variant of kidney allogenic graft rejection associated with long-term graft loss. Since then, the scientific community tries to establish optimal scheme of diagnostic methods and therapeutic approach.

Keywords: chronic active T-cell mediated rejection ; kidney rejection ; Banff classification ; kidney transplantation

1. Assessment of Efficiency of Current and Previous Treatment Methods

Kidney transplantation (KT) is the best method for kidney replacement therapy (KRT) because of high patient survival rates and quality of life (QoL) [1]. Nonetheless, this treatment requires immunosuppressive therapy and currently the occurrence of chronic active (CA) T-cell mediated rejection (TCMR) is being associated by the scientists with insufficient immunosuppression [2]. It is linked with the presence of characteristic lesions such as interstitial fibrosis and tubular atrophy (i-IFTA) which suggests that immunosuppressive therapy could be beneficial for patients as a treatment method [3]. Nonetheless, the preferential treatment method hasn't been established yet and various clinical studies are being performed.

Basing on recent research, the medications which can be potentially helpful in CA TCMR treatment are methylprednisolone (MP, 4 mg/d), tacrolimus (Tac, minimal concentration 5–8 ng/mL), mycophenolate mofetil (MMF, 500–1500 mg/d), basiliximab (20 mg in days 0 and 4), everolimus (EVR, minimal concentration 3–8 ng/mL) and anti-thymocyte globulin (ATG). According to clinical case reports combining doses of maintenance oral immunosuppressive agents such as Tac, MMF, MP and EVR with ATG administration together with steroid pulse therapy may give promiscuous results. In the outcome of the treatment in some cases part of lesions characteristic for CA TCMR subsided and in none of 3 patients a deterioration of eGFR was observed [4].

Different studies have shown that only in a small subset of cases the improvement in kidney function in patients suffering from CA TCMR can be achieved with immunosuppression. Treatment provided in that research consisted of 500 mg i.v. of methylprednisolone for 3 days followed by oral administration of prednisone 5 mg daily dose for over 4 weeks. In addition, if the stage of CA TCMR was IB, the treatment was combined with ATG (1.5 mg/kg daily for 4 days). Only 20% of patients achieved at least 50% eGFR recovery at 4 weeks after biopsy. The association between the stage of CA TCMR and treatment response was noticed. Patients with grade IB tended to have a lower response than the ones with IA grade of CA TCMR. In addition, the observed response rate was better in patients who didn't meet criteria for co-existing acute TCMR what suggests that treatment response is not linked with the treatment of acute TCMR. No significant difference was noticed between patients with severe, moderate, or mild parenchymal scarring in biopsies. Nonetheless, increased immunosuppressive therapy may be contraindicated in some cases where criteria for acute TCMR are not met and severe parenchymal scaring is recognized [3].

Studies presented above were performed on a modest group of patients and as a result of this fact, discovered findings cannot be conclusive for establishing criteria for treatment of CA TCMR. Yet, achieved results seem to be inquisitive and need further investigation.

2. Immunosuppression in Treatment of CA TCMR

Some clinicians hesitate about the treatment of CA TCMR because of the possible risks of immunosuppressive therapy. One of the possible medication groups to prevent graft from rejection are calcineurin inhibitors such as tacrolimus, which are characterized by excellent short-term therapeutic results. However, the chronic nephrotoxicity of these medications is

the major disadvantage of present immunosuppressive regimens. A significant relationship between the concentration and the toxicity or possible rejection was noticed. Ranges noted in the research are very broad from 5 to 25 ng/mL, depending also on the time after transplantation. All those observations possibly suggest that these medications have a very narrow therapeutic window and doses should be differently chosen depending on each patient's various conditions [5]. In another research the association was observed between graft tacrolimus concentration and nephrotoxicity (828 pg/mg tissue) [6].

Factors which contribute to its side effects include tacrolimus' systemic levels; exposure to metabolites of tacrolimus, local renal exposure to tacrolimus; local vulnerability factors for calcineurin inhibitors (CNI) nephrotoxicity such as age of a kidney, local hepatic, and intestinal cytochrome P450A3, local renal P-glycoprotein and renin-angiotensin-aldosterone (RAA) system activation. Potentially nonreversible nephrotoxicity of tacrolimus may lead to kidney graft loss and its diagnosis should be made after exclusion of any different causes of allograft dysfunction and also with reference to the clinical context [7].

There are available other immunosuppressive treatments such as MMF which is deprived of nephrotoxicity. Its mechanism of action is based on depletion of guanosine nucleotides in T and B lymphocytes and also the inhibition of their proliferation. As a result, MMF suppresses not only cell-mediated immune response but also antibody formation. Because of this mechanism, MMF decreases both acute and chronic rejection in graft recipients and likewise can be used in some other nephropathies [8].

Another medication which can be possibly used in the treatment of CA TCMR is ATG. It is administered mostly for steroid-resistant TCMR. However, basing on small clinical study it is encouraged for the prompt usage upon CA TCMR diagnosis [4]. On the other hand, the high probability of undesirable events including neutropenia and Cytomegalovirus (CMV) antigenemia often results in the stoppage of escalated immunosuppression. The conclusion is that ATG administration often needs CMV prophylaxis with the use of Valganciclovir (VGCV) [9]. It suggests that every patient, especially ones with high risk of infection and in danger of neutropenia, requires a customized treatment strategy.

3. The Revision of the Need of CA TCMR Treatment

After the Banff 2017 conference where CA TCMR criteria were revised the study was performed to assess if CA TCMR is diagnosed and treated worldwide. It has proven that CA TCMR was diagnosed in more than 90% of cooperating clinical centers and treated with steroids or other immunosuppressive medications in more than 80% of cases. Precisely 36% of cases were treated routinely, 49% under condition and 15% rarely. Those clinicians who treated CA TCMR under condition depended the therapy on the score i and v in the Banff lesion score (49%), on the lack of severe IFTA (47%) or on the cause of biopsy (4%). Doctors who hesitated to provide the treatment referred to the lack of clinical data (64%), some believed that risk outweighs benefits or pointed out the experience of ineffectiveness (27%). In addition, in 9% of cases, pathologists did not diagnose CA TCMR at all.

Patients were treated mostly with steroids (25%), 18% with steroids combined with ATG if the grade of illness was diagnosed as IB, 17% with increased baseline immunosuppressants and 16% with ATG if there was no response for steroids treatment [10]. It is observed that treatment of CA TCMR/i-IFTA can improve kidney function. Based on these observations i-IFTA cannot be considered as an irreversible nonspecific lesion of the tissue. Instead, it should be seen as an ongoing, active tissue injury susceptible to treatment in the proper context of the underlying inflammatory process [11].

There is a possible relationship between CA TCMR and preceding acute TCMR, mixed antibody-mediated rejection (ABMR) with acute TCMR or active AMBR. It was examined that 55% of treated CA TCMR matched those criteria. The share of responders was not suggestively different between patients with and without prior episodes of rejection. It was examined that 30% of treated recipients had donor-specific antibodies even though they didn't meet the Banff 2017 criteria for ABMR. It seems that the association to prior rejection is a complex phenomenon in an evaluation of biopsies from the kidney allograft function studies cohort. Although former rejection was more often observed in i-IFTA, the majority of CA TCMR biopsies did not have preceding acute rejection and no type of rejection was more common than others [12].

It is crucial to compare acute TCMR, i-IFTA attributable to other diseases like ABMR or recurrent glomerulonephritis and IFTA without inflammatory process to assess if immunosuppressive treatment of CA TCMR is related to its T cell mediated immunologic pathomechanism or if it represents nonspecific anti-inflammatory mechanism on any form of i-IFTA. It could potentially be advantageous in assessment of determination of immune mediated mechanisms of injury which can be treated by immunosuppressive therapies versus mechanisms which are not immunological mediated which seem to be more resistant to therapy [11].

Current findings put the spotlight on new treatment methods including the application of nanoparticles in patients with kidney grafts or other kidney diseases. The use of nanoparticles may reduce and prevent ischemic reperfusion injury, more efficiently deliver the drug to the transplant site while avoiding systemic effects and also accurately identify and visualize the affected area. By making it possible, it has the potential to revolutionize kidney transplantation [13].

Although some clinical research were performed and results are promiscuous, there is still a need for big, randomized research where patients would be treated with various immunosuppressive agents and combinations of those medications to work out an optimal scheme of CA TCMR treatment.

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