Tocilizumab in a patient affected by chronic active antibody-mediated rejection; histological improvement, reduction of proteinuria and renal function stabilization

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ABSTRACT

Introduction: Chronic active antibody-mediated rejection (cAMR) is a significant and rapid destructive form of allograft rejection and it is related to donor specific antibodies (DSA). Interleukin 6 (IL-6) plays an important role in mediating the allograft rejection by promoting CD4+ T cells differentiation to Th17 phenotype while inhibiting Treg. Tocilizumab is a humanized monoclonal antibody directed to IL-6 receptor (IL-6-R). The aim of the study is to demonstrate the efficacy of tocilizumab as rescue therapy for cAMR.

Case Presentation: A 50-year-old man with Alport syndrome and with positive DSA against B7 e B55 underwent a second kidney transplant (HLA 2 mismatch). He received thymoglobulin and three plasma exchanges as induction therapy. Proteinuria (1-1.3 g/24 h) and decline in kidney function (serum creatinine; 1.5 mg/dL) appeared at 9 months. Kidney biopsy showed endocapillary proliferation, mononuclear cells infiltration, glomerular basal membrane duplication and tubulitis suggestive of cAMR. The patient has been treated with tocilizumab (6 mg/kg/mon) for six months. Reduction of proteinuria (0.6 g/24 h) and mild improvement of kidney function (serum creatinine; 1.3 mg/dL) were observed after tocilizumab treatment. A second biopsy revealed a significant decrease of glomerulitis and peritubular capillaritis. A significant reduction in DSA was detected.

Conclusion: Inhibition of the IL-6 receptor by tocilizumab may represent a novel and cheering approach to treat cAMR.

Implication for health policy/practice/research/medical education:
Chronic active antibody-mediated rejection (cAMR) is a significant and rapid destructive form of allograft rejection, where IL-6 plays an important role. We report a case of 50-year-old man with kidney transplant, who developed cAMR and has been treated with tocilizumab, a humanized monoclonal antibody directed to IL-6 receptor (IL-6R). We demonstrate its efficacy as new treatment strategy in patients who are resistant to current therapies.

Case Presentation

A 51-year-old obese male underwent a second kidney transplant in 2018. The patient’s history shows microhematuria and hearing loss from childhood secondary to Alport syndrome. He had been on hemodialysis from the age of 17 years old. His first kidney transplant was performed in 1990, but because of an early failure, he started again the hemodialysis treatment three years later, in 1993.

In the period following the transplant, the patient contracted viral hepatitis B, for which he is still being treated with Lamivudine. In 2012, adenocarcinoma of the colon was diagnosed during an ordinary screening, reason why he was suspended from the waiting list for 5 years.

In May 2018, the patient underwent a second kidney transplant. The donor was a deceased 51-year-old female; cold ischemia lasted 13 hours and the transplant was complicated by delayed graft function. Induction therapy was made by basiliximab, thymoglobulin (3 mg/kg), three plasmapheresis/plasma exchange (PLEX) and pulse steroid. The maintenance therapy was composed of tacrolimus (TL between 6-8 µg/dL for the first year), mycophenolate mofetil (MMF) and steroid. Renal function was mildly depressed at discharge (serum creatinine: 1.6 mg/dL).

At the time of the second transplantation, immunology tests showed two mismatches for HLA and the presence of anti-HLA antibodies directed against DR 53 (fluorescence intensity (MFI) pre-kidney transplant 15000).

DR 53 is considered a “public superantigen”, because it shares some epitopes with other HLA class II antigens (DR4, DR7, DR9), but donor-specific anti-HLA-DR53 antibodies are not considered an exclusion criteria in the algorithm for the transplant candidate selection. The donor presented a DR 7 antigen.

After 9 months from kidney transplant, we noted a slight increase in proteinuria (from 0.5 to 1.3 g/24 h), and a mild deterioration of renal function (serum creatinine from 1.3 to 1.5 mg/dL). The research for DSA confirmed only a high rate of anti-HLA-D53 [fluorescence intensity (MFI) 15000-16000]. Thus, we decided to perform a renal biopsy.

The histological report showed a cAMR. Light microscopy examination revealed severe chronic transplant glomerulopathy, glomerulitis and focal severe peritubular capillaritis. The biopsy also showed T-cell infiltrate underneath thickened sub-endothelial space of an interlobular artery, consistent with chronic transplant arteriopathy, and focal interstitial T-cell dominant inflammation with moderate tubulitis (Figure 1A and 1B). C4d deposition in peritubular capillaries was negative.

The usual therapy of cAMR consists of reducing the antibody levels by rituximab + immunoglobulins + plasma exchanges, but it is often resistant to such therapies. Hence, we decided to start the treatment with tocilizumab (RoActemra at a dose of 6 mg/kg) after premedication with steroids [methylprednisolone 60 mg (intravenous; i.v.)], paracetamol, and chlorphenamine in our “Day hospital”, with constant monitoring of vital signs during the sixty-minute infusion time.

Before the initiation of tocilizumab, the patient was tested for HBV–DNA (neg.), HCV and HIV serology, and Quantiferon-TB. Prophylactic antiviral therapy with acyclovir (200 mg/d) and Pneumocystis Carinii prophylaxis with trimethoprim-sulfamethoxazole (160 plus 800 mg; half a tablet three times a week) was established. During the treatment period (one year) we observed two adverse events; a transient increase of HBV–DNA (1190 IU/mL), treated with entecavir (tablet 0.5 mg/d), and an episode of pneumococcal pneumonia.
responsive to antibiotic therapy.

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On follow-up, renal function and 24-hour proteinuria were monitored. Figure 2 shows renal function and 24-hour proteinuria, before and after tocilizumab.

After 6 months of tocilizumab treatment, we repeated a renal biopsy: the glomeruli showed a thickening and a reduplication (chronic transplant glomerulopathy) of basement membranes but no significant glomerulitis. Inflammatory infiltrate was mostly interstitial with only mild and focal peritubular capillaritis (Figure 1C-D). After 12 months, in addition to a clear histological improvement, we observed a functional renal stabilization and a persistent reduction of proteinuria (Figure 2), and we assisted to a reduction in DSA (MFI 15000 pre-tocilizumab, MFI 7500 post-tocilizumab (Figure 3).

**Discussion**

IL-6 consists of 184 amino acids and was originally identified by Narazaki and Kishimoto (4) as B-cell stimulatory factor 2. In healthy subjects, this cytokine is not expressed, but it is rapidly synthetized by tissue injury, as observed in chronic immune disorders (rheumatoid arthritis, systemic juvenile idiopathic arthritis, and polyarticular juvenile rheumatoid arthritis), transplant rejection and graft versus host disease (5). In the kidney, IL-6R is present on mesangial cells and IL-6/IL-6R cassette is associated with mesangial cell proliferation, which seems to play a pathological role in the progression of experimental crescentic glomerulonephritis. In abnormal renal tissue, IL-6R is expressed on the surface of podocytes, tubular epithelial cells and arterial smooth muscle cells.

Clinical observations and animal models have demonstrated that IL-6 plays an important role in mediating the allograft rejection. IL-6 production is responsible for allogenic T-cells infiltration (6), while its inhibition with anti-IL-6R induces graft acceptance, in combination with costimulatory pathway blockage by CTLA-4 (cytotoxic T-lymphocytes associated protein 4) (7). B-cells that infiltrate the allograft produce massive pro-inflammatory cytokines, including IL-6, that can induce interstitial fibrosis and tubular atrophy (IF/TA). Circulating IL-6 activates cells by binding to the nonsignaling membrane receptor (IL-6R). The IL-6/IL-6R cassette then activates cellular gp 130, which triggers the signaling transduction pathway that ultimately results in JAK/STAT activation and gene transcription events (8).

Other data from animal models have demonstrated an important role in the mediation of allograft vasculopathy.
(9). Using a murine aortic interposition model of vascular rejection, donor-derived IL-6 amplifies allogenic T cell response that causes vascular rejection. Moreover, it is known that endothelial cells produce IL-6 as a major factor responsible for intimal proliferation. In summary, cytokines are essential in host defense and maintenance of tissue homeostasis, but abnormal or excessive IL-6 overexpression results in inflammation and tissue injury. Disruption of signaling pathways limits inflammation by inhibiting cell activation and expansion of effector cells, thus reducing chronic immune activity.

Long-term outcomes of patients with cAMR is very poor with a median graft survival of 1.9 years. The conventional “standard care therapies” (PLEX, IV-Ig and rituximab) are often disappointing and associated with higher risk of infectious complications which are particularly insidious in immunosuppressed patients.

Choi et al (10) in 2017 treated with tocilizumab 56 pts with cAMR plus DSAs and transplant glomerulopathy who failed standard care treatment. They demonstrated graft survival rates of 80% at 6 years with a stabilization of renal function at two years. Moreover, Lavacca et al (11) in 2020 adopted tocilizumab as a first-line approach in cAMR, showing early serological and histological improvement as demonstrated by protocol biopsies.

In our case, we decided to maintain the same chronic immunosuppression therapy and to associate tocilizumab, without prior standard therapy for cAMR. The control biopsy, after six months of tocilizumab, demonstrated a clear amelioration of glomerulitis and capillaritis. It is possible that the beneficial effects seen on glomerular compartment were due to the blockage of IL-6 local production by mesangial cells, which also express IL-6 receptor. Moreover, Lavacca et al (11) observed an increased expression of three genes (TJP-1, AKR1C3 and CASK) that are upregulated by tocilizumab treatment and that stimulate the regeneration of podocytes, mesangial and tubular cells. Because a rebound of IL-6 activity was demonstrated after stopping tocilizumab in desensitization protocol (12), we decided to continue tocilizumab, achieving a constant stabilization of renal function and a persistent reduction of proteinuria and DSA.

Conclusion
This case presentation showed that further studies are needed with rigorous clinical trials setting, but tocilizumab may represent a valid alternative to the management of cAMR.

Authors’ contribution
LP, DR and MA were the principal investigators of the study. LP, DR, MA, MT, MD and MM were included in preparing the concept and design. LP and DR rechecked the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest
Authors declare no conflict of interests

Ethical considerations
The use of tocilizumab was conducted in consideration of ethical issues in accordance to the Helsinki Declaration and was approved by both internal Ethical and Pharmaceutical Committees. The patient gave written informed consent after description of the potential risks and benefits of tocilizumab.

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References
Tocilizumab in chronic active rejection


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