Editorial paper

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Treatment of rheumatic diseases in patients after organ transplantation

Michał Ciszek, Magdalena Durlik

Department of Transplantology, Immunology, Nephrology and Internal Diseases, Medical University of Warsaw, Warsaw, Poland

The utilization of classical and biological disease-modifying antirheumatic drugs (DMARDs) for treating rheumatic diseases in organ transplant recipients presents two main challenges. Firstly, how can DMARDs be incorporated into primary immunosuppressive therapy without increasing the risk of adverse effects? Secondly, can one of the immunosuppressive drugs be replaced with a DMARD without raising the risk of organ rejection?

Unfortunately, no randomized, prospective studies are available, and the majority of the data is derived from observational, usually retrospective series of clinical cases.

Classical post-transplant immunosuppression is generally effective in maintaining remission in systemic lupus erythematosus (SLE) or vasculitis. However, challenges arise in treating other rheumatic diseases, as the standard immunosuppression used in transplantation may not effectively control the inflammatory process. Moreover, both synthetic and most biological DMARDs have not been employed in the treatment after organ transplantation.

Synthetic disease-modifying antirheumatic drugs

Methotrexate

Reports of the use of methotrexate (MTX) in combination with standard immunosuppression after transplantation are sporadic, mainly in the treatment of graft vs. host disease in hematopoietic cell transplant patients, where it was used in combination with calcineurin inhibitors and mycophenolic acid (MPA) at a reduced dose [1]. The risk of MTX adverse reactions is increased in patients with reduced estimated glomerular filtration rate (eGFR) < 45 ml/min/1.73 m^2 [2]. Hepatotoxicity of MTX should also be considered, but there are no data to assess this risk in patients after liver transplantation. No specific recommendations can be made, but the drug is relatively contraindicated for liver recipients or kidney transplant recipients with reduced eGFR.

Hydroxychloroquine

The use of hydroxychloroquine (HCQ) together with standard immunosuppression did not reduce the rate of renal rejection in transplanted patients with SLE, but also did not increase the risk of serious infections [3]. However, including HCQ may increase the risk of ventricular arrhythmias and pancytopenia [4]. It seems that HCQ can be safely added to standard organ transplant treatment, but patients with an increased cardiac risk (prolonged electrocardiogram QT interval, complex arrhythmias) should be excluded.

Leflunomide

The immunosuppressive and antiviral properties of leflunomide (LEF) offer potential benefits in organ transplantation. Metabolism and excretion of the drug primarily occur through the bile, which may present challenges after liver transplantation. There are several publications describing the use of LEF after kidney transplantation in ganciclovir resistant cytomegalovirus (CMV) infection and BK nephropathy [5, 6]. Notably, no increased risk of graft rejection was reported, with the main adverse effects being related to hepato- and myelotoxicity. It appears that LEF may serve as an alternative to MPA derivatives in patients with rheumatic conditions following organ transplantation. Regular monitoring of the LEF metabolite's therapeutic levels is advisable [7].

Janus kinase inhibitors

Phase IIb clinical trials conducted with tofacitinib in combination with mycophenolate mofetil and glucocorticosteroids after renal transplantation showed that

Address for correspondence:
Michał Ciszek, Department of Transplantology, Immunology, Nephrology and Internal Diseases, Medical University of Warsaw, 59 Nowogrodzka St., 02-006 Warsaw, Poland, e-mail: michal.ciszek@wum.edu.pl

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such treatment reduced the frequency of acute rejection. However, the main issue was the adverse side effects, particularly bone marrow suppression and infections, which led to the discontinuation of further research [8].

Biological disease-modifying antirheumatic drugs

Data on the usage of biological DMARDs are primarily derived from systematic reviews and meta-analyses. Predominantly, these data pertain to post-liver transplant patients undergoing treatment for inflammatory bowel disease (IBD). The risk of rejection is lower in liver than in kidney transplantation. Immunosuppression after liver transplantation often relies on tacrolimus monotherapy, allowing for a safer reduction in the strength of immunosuppression after starting a biological DMARD.

In a meta-analysis of 55 studies involving 177 patients (141 liver, 42 kidney), use of tumor necrosis factor inhibitors (TNFi) (81.4%), vedolizumab (23.7%) and anakinra (7.3%) was assessed. The predominant complications were pyelonephritis (12 cases), *Clostridioides difficile* (18 cases), and CMV infections (7 cases). A total of 16 patients were diagnosed with cancer, including colon cancer (4 cases), skin cancer (4 cases), and post-transplant lymphoproliferative disorder (3 cases). Patients' age, gender, and immunosuppression were not found to be associated with the risk of infections. Acute rejection was observed in 5 cases (4 kidney graft). Clostridioides difficile infection and colorectal cancer occurred in patients secondary to IBD [9].

Tumor necrosis factor inhibitors

In a retrospective multicenter study examining the effects of TNFi in renal transplant recipients, clinical improvement was evident in 13 out of 16 patients. Among the cohort, 8 patients experienced severe infectious complications, predominantly pyelonephritis ($n = 6$) and viral infections ($n = 3$), and one patient experienced graft loss due to antibody-mediated rejection (ABMR). Furthermore, 4 patients were diagnosed with cancer. Upon univariate analysis, recipient age showed an association with both mortality and the development of infections. The authors concluded that anti-TNF therapy is effective but must be used with caution, especially in older patients [10].

Rituximab

Rituximab (RTX) is an essential component of the standard treatment for ABMR of a transplanted organ. The drug is also used in the treatment of membranous glomerulonephritis in a transplanted kidney, with the effectiveness above 80% [11]. In most studies, RTX is added to standard immunosuppression. The use of RTX is associated with a higher frequency of bacterial and viral infections. One study found an increased incidence of death from infection, but no increased incidence of cancer was observed [12].

Tocilizumab

Interleukin-6 receptor blockers, specifically tocilizumab (TOC) and clazakizumab, were also investigated in the treatment of antibody-mediated rejection following renal transplantation. Tocilizumab was initiated for cases that had shown an inadequate response to conventional treatment, including RTX, and was adjunctive to standard immunosuppression in the majority of the studies. A systematic review of 7 studies involving 117 renal transplant recipients treated with TOC revealed that the most common adverse reactions were viral and bacterial infections but their incidence did not exceed that observed in the RTX groups. Tocilizumab was administered at a monthly dosage of 8 mg/kg, with a maximum dose of 800 mg for a duration of 12 months [13].

Anakinra

Anakinra (ANK) was used mainly in a patient after kidney transplantation with Mediterranean fever at a dose of 100 mg/day, without a reduction in primary immunosuppression. While there was no increase in the risk of serious infectious complications compared to the control group, infection-related deaths were more frequent in the study group [14]. In another study, the incidence of infectious complications after ANK was lower compared to TNFi [15].

Conclusions

Hydroxychloroquine and LEF demonstrate relative safety in organ transplant recipients. When considering treatment with biological DMARDs, it seems advisable to use drugs already investigated after transplantation, such as RTX and TOC. Anakinra appears to be a relatively safe option for post-transplant patients based on the available data. Unfortunately, specific recommendations for potent medications such as MTX and TNFi agents are challenging to formulate, so their use should be reserved for exceptional cases.

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