Case Reports in Nephrology and Dialysis

Case Rep Nephrol Dial 2021;11:10–15

DOI: 10.1159/000510842
Published online: January 27, 2021

Single Case

A Case of *Pneumocystis jirovecii* Pneumonia under Belatacept and Everolimus: Benefit-Risk Balance between Renal Allograft Function and Infection

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Keywords
Pneumocystis · Belatacept · Antibiotic prophylaxis · Iatrogenic · Anti-rejection therapy

Abstract
Pneumocystis jirovecii pneumonia is an opportunistic disease usually prevented by trimethoprim-sulfamethoxazole. A 49-year-old HLA-sensitized male with successful late conversion from tacrolimus-based to belatacept-based immunosuppression developed *P. jirovecii* pneumonia for which he presented several risks factors: low lymphocyte count with no CD4+ T cells detected since 2 years, hypogammaglobulinemia, history of acute cellular rejection 3 years before, and immunosuppressive treatment (belatacept, everolimus). Because of respiratory gravity in the acute phase, the patient was given oxygen, corticosteroids, and trimethoprim-sulfamethoxazole. Thanks to the improvement of respiratory status, and because of the renal impairment, trimethoprim-sulfamethoxazole was converted to atovaquone for 21 days.

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Indeed, after 1 week on intensive treatment, the benefit-risk balance favored preserving renal function according to respiratory improvement status. *P. jirovecii* pneumonia prophylaxis for the next 6 months was monthly aerosol of pentamidine. Long-term safety studies or early/late conversion to belatacept did not report on *P. jirovecii* pneumonia. Four other cases of *P. jirovecii* pneumonia under belatacept therapy were previously described in patients having no *P. jirovecii* pneumonia prophylaxis. Studies on the reintroduction of *P. jirovecii* pneumonia prophylaxis after conversion to belatacept would be of interest. It could be useful to continue regular evaluation within the second-year post-transplantation regarding immunosuppression: T-cell subsets and immunoglobulin G levels.

Introduction

Pneumocystis jirovecii pneumonia (PJP) is an opportunistic infection that often develops in immunocompromised kidney-allograft recipients [1]. Several risks factors have been described: age, cytomegalovirus (CMV)-positive viremia, neutropenia, a lymphocyte count of <750/mm^3 for more than 1 month (although a CD4+ T-cell of <200/μL is not a good biomarker in non-HIV patient), low plasma total gamma globulins, an acute-rejection episode, and immunosuppression treatment [2].

Renal toxicity was previously well described with high dose of trimethoprim-sulfamethoxazole (TMP-SMX) used in PJP treatment, i.e. acute tubular necrosis. SMX acts as a nephrotoxic agent through tubular precipitation and local production of crystal. Renal impermeant was also reported whatever the dose used, i.e. acute interstitial nephritis with immunologically induced hypersensitivity [3, 4]. Therefore, several studies have assessed the use of atovaquone or pentamidine to prevent PJP [5, 6]. Although the results are promising, TMP-SMX is still the first-choice prophylaxis [7]. In fact, the use of TMP-SMX as a prophylactic drug for PJP for 6–12 months after kidney transplantation can significantly decrease its incidence [8].

Herein, this case report describes the management and prevention of PJP in a kidney-allograft recipient receiving maintenance immunosuppressive therapy of belatacept, everolimus, plus corticosteroids.

Case Report

A 49-year-old HLA-sensitized male had end-stage renal disease that was secondary to autosomal dominant polycystic kidney disease, which had first been diagnosed when he was aged 30 years. In 2012, he received peritoneal dialysis for 1 year, and then hemodialysis for 2 years. He then received a kidney transplant in 2015 from a deceased donor. The donor and recipient were both CMV seronegative. The initial induction therapy was based on antithymocyte globulins (Thymoglobulin®, 0.5 mg/kg/day for 5 days) plus a maintenance immunosuppressive regimen of tacrolimus, mycophenolate mofetil (MMF), and corticosteroids. Serum-creatinine level at 1 month post-transplantation was 194 μmol/L.

At 3 months post-transplantation, serum creatinine had increased to 325 μmol/L, and the histology showed acute cellular rejection, which was treated with 3 boluses of methylprednisolone (10 mg/kg each). Despite the disappearance of inflammatory infiltrates within the

interstitium (as seen in a follow-up allograft biopsy), renal function remained altered (creatinine at 319 μmol/L). In January 2017, the patient was converted to a belatacept-based calcineurin-free regimen, which led to recovery of renal function in 18 months: serum-creatinine level became 212 μmol/L. In August 2018, MMF was switched to the antiproliferative drug everolimus because of the risk of developing squamous-cell carcinoma. In December 2018, the patient developed a dry cough with a purulent sputum, although the fever resolved after 7 days of receiving amoxicillin. However, a few days later, he developed progressive and severe dyspnea, which led to his hospitalization 2 weeks later. In a clinical examination, the patient had tachypnea (32 breaths/min), and oxygen saturation was only at 88% in room air. Chest computed tomography showed diffuse bilateral alveolo-interstitial opacities suggesting an opportunistic infection (Fig. 1). The initial blood investigations revealed the following: C-reactive protein, 58 mg/L; low lymphocyte count (0.4 g/L) with no CD4 +T cells detected for 2 years; and hypogammaglobulinemia, i.e. immunoglobulin G (IgG) was 3.2 g/L compared to 4.2 g/L 5 months previously. *Legionella*, *Aspergillus*, and *Pneumococcus* antigenemias, *Chlamydia*, and *Mycoplasma* serologies, and a CMV DNAemia were all negative. Samples from a bronchoscopy and a bronchoalveolar lavage were negative for bacterial and viral pathogens (cultures and PCR testing) but revealed a high load of *P. jirovecii* DNA.

Because of respiratory gravity (i.e., PO_2 = 60 mm Hg), the patient was given continuous oxygen support, intravenous corticosteroids (a single dose of 1 mg/kg of methylprednisone, which was then decreased to 0.5 mg/kg), and TMP-SMX (800/160 mg adjusted according to renal function).

After receiving these therapies for 7 days, the patient was weaned off oxygen, and his biological inflammatory markers were improved; however, there was 20% degradation in renal function (shown in Fig. 2). Because of the improved respiratory status but also the renal impairment we converted TMP-SMX to atovaquone for 21 days. The patient could then return home after 9 days of hospitalization with stable renal allograft function (creatinine: 227 μmol/L). Follow-up investigations showed normalization of CRP level, and renal allograft function returned to baseline values (creatinine: 200 μmol/L), and improvements were seen on radiological images. PJP prophylaxis for the next 6 months was pentamidine given as an aerosol monthly in the hospital. Belatacept (5 mg/kg every 4 weeks) was never stopped.

Discussion/Conclusion

At 3 years after renal ABO- and HLA-compatible allograft, and 2 years after conversion from tacrolimus to belatacept, our patient had developed acute PJP. He had presented several risks factors: immunosuppressive treatment (belatacept and everolimus), history of acute cellular rejection at 3 months post-transplantation, biological evidence of overimmunosuppression, i.e. low lymphocyte count with no CD4 T cell and decrease in IgG at 3.2 g/L. Indeed, antithymocyte globulins result in long-term lymphopenia. Crepin et al. [9] have reported that ATG delays thymic-dependent T cell reconstitution, increases the frequency of late-stage differentiated T cells, and promotes peripheral Treg expansion. Moreover, ATG is associated with persistent low values of T-cell relative telomere length and telomerase activity. Taken together, these data suggest that ATG induces accelerated immune senescence.

Hughes et al. [10] compared treating acute PJP with atovaquone or TMP-SMX. Patients treated with atovaquone "more often had no response" and had a higher mortality rate (7 vs. 0.6%, p = 0.003). Thus, TMP-SMX was the first treatment recommended to treat acute PJP [7].

At admission, our patient presented with acute-phase PJP with gravity criteria (he needed oxygen: PO_2 = 60 mm Hg): at that time, the benefit-risk balance favored an aggressive induction treatment. Nevertheless, after 1 week, the benefit-risk balance became reversed in favor of preserving renal function according to respiratory improvement status. Thus, our patient was switched to receive atovaquone instead. After the induction treatment, he received pentamidine as the prophylaxis.

Belatacept, a new costimulation blocker has attracted interest as a treatment to preserve renal function, and improved cardiovascular/metabolic risk profile without infectious alarm signal confirmed by Vicenti and al. [11] after 7 years of use. Specific studies about early [12] or late [13] conversion to belatacept did not report PJP. The first case of lethal PCP under belatacept was described by Haidinger et al. [14] 4 years after transplantation in a multi-infected patient. Then, three other cases of PCP under belatacept were reported in ABO-incompatible transplantation [1]. A recent study showed that 34/280 patients had presented opportunistic infection after conversion to belatacept, 28.6% represented PJP, i.e. 10 patients about 10 months after conversion to belatacept (50% of early conversion). All these patients were without prophylaxis, and the mortality reached 33.3% [15]. This study also proposed to consider as a risk factor of opportunistic infection the estimated glomerular filtration rate (eGFR) at the time of belatacept conversion: the higher the eGFR, the lower the risk of infection. Even if PJP was documented under belatacept treatment, this treatment alone cannot be fully responsible for the infection of the patient. Indeed a few months after being converted from tacrolimus to belatacept, MMF was replaced by everolimus. It has been reported that everolimus-based therapy can induce interstitial lung diseases (ILD). In a retrospective series of 500 kidney-transplanted patients, Solazzo et al. [16] found 26 ILDs; of these, 12 cases (46.2%) were from infections (42.8% by *P. jirovecii*), whereas in 14 cases (53.8%) this was related to drug-induced ILD. Finally, there were other facilitating factors such as overimmunosuppression, chronic T-cell lymphopenia, and previous episode of treated acute rejection.

Even though the risk of opportunistic infections resides mostly within the first year post-transplant, the second year after transplantation seems to be still a high-risk period for developing PJP [2]. However, the actual duration of PJP prophylaxis varies between 6 and 12 months post-transplantation; because of this risk within the second year, the duration of prophylaxis should be reevaluated. Goto et al. [17] proposed long-term PJP prophylaxis using TMP-SMX, based on the three outbreaks of PJP they reported in patients who had stopped PJP prophylaxis after 3 months of treatment.

Before considering long-term prophylaxis of PJP using TMP-SMX, it would be helpful to have more data on renal toxicity after long-term exposure to TMP-SMX. Another option could be to conduct studies on reintroduction of PJP prophylaxis after a switch from calcineurin inhibitor-based to belatacept-based therapy. In particular, prophylaxis using a treatment that would not cause renal toxicity, such as monthly aerosol of pentamidine, could be assessed further. Currently, a compromise could be to continue regular biological evaluations in the second year after renal allograft transplantation regarding immunosuppression: lymphocytes, CD4+ T-cell counts, and IgG levels, even if the transplant was ABO and HLA compatible.

Statement of Ethics

Written informed consent for publication (including figures) was obtained from the patient, and the research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

None.

Author Contributions

Q. Perrier contributed to acquisition of data and writing of the manuscript. R. Tetaz and L. Rostaing provided supervision and mentorship. All the authors approved the final manuscript.

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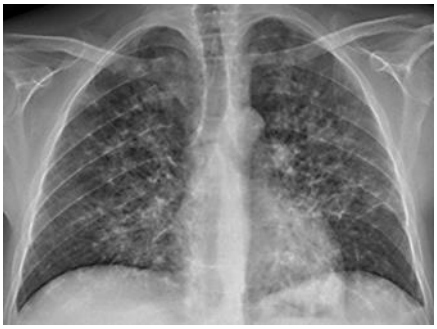

Fig. 1. Bilateral chest X-ray with alveolo-interstitial opacities.

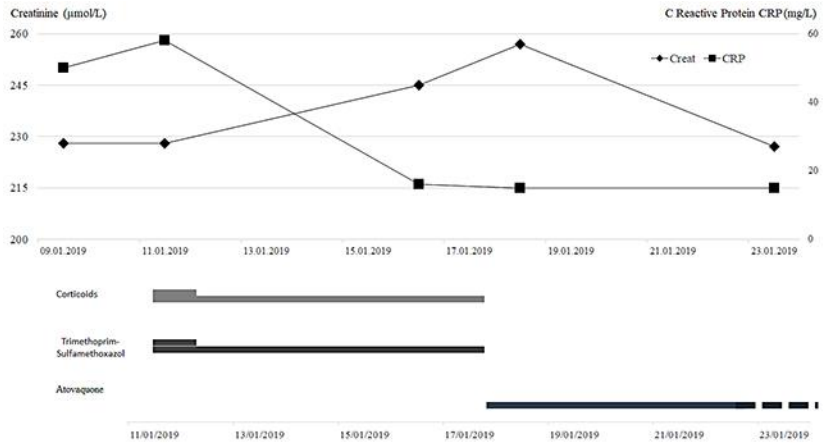

Fig. 2. Evolution of biological markers linked to the management of *Pneumocystis jirovecii* pneumonia.