Infection (2012) 40:473–475
DOI 10.1007/s15010-012-0277-y

CORRESPONDENCE

Duration of prophylaxis with trimethoprim–sulfamethoxazole in patients undergoing solid organ transplantation

P. Malhotra · S. D. Rai · D. Hirschwerk

Received: 24 October 2011 / Accepted: 25 May 2012 / Published online: 12 June 2012

Patients undergoing solid organ transplantation (SOT) are at risk for opportunistic infections. Prophylaxis with trimethoprim–sulfamethoxazole (TMP-SMX) has been widely used after SOT for the prevention of opportunistic infections, including *Pneumocystis jirovecii* (PCP). The drug has the added benefit of preventing infections with *Toxoplasma gondii*, *Isospora belli*, *Cyclospora cayetanensis*, *Nocardia* sp., *Listeria* sp., and many bacterial pathogens that may cause urinary, gastrointestinal, and respiratory infections [1].

The recommended duration of TMP-SMX prophylaxis varies among centers that perform transplant operations and is dependent upon the type of organ transplanted, perceived degree of immunosuppression, episodes of rejection, and history of any prior opportunistic infections.

Most centers administer TMP-SMX prophylaxis after renal transplantation for a period of 3–6 months [1]. Lifelong prophylaxis is recommended at many centers after heart, liver, and lung transplantation [2].

The recommendations of the American Society of Transplantation (AST) are for PCP prophylaxis to be administered after SOT in centers having a prevalence of 3–5 % for 6–12 months post-transplantation. In patients with lung, small bowel transplants or those with prior PCP or chronic cytomegalovirus (CMV) disease, lifelong prophylaxis may be indicated [3].

Heart transplant recipients who are at high risk for disseminated toxoplasmosis (donor seropositive and recipient seronegative) receive prophylaxis such as pyrimethamine–sulfadiazine instead of TMP-SMX for the first 6 months [4].

We briefly present two cases of renal transplant recipients who received the "recommended duration of prophylaxis" but developed PCP and central nervous system (CNS) toxoplasmosis, respectively, after their TMP-SMX treatment was discontinued.

A 43-year-old Hispanic woman who had end-stage renal disease secondary to hypertension had undergone living related donor renal transplantation 13 months prior to presentation. The patient received antithymocyte globulin (ATG) induction prior to the transplant. Three months after transplant, the patient was treated for an episode of acute rejection with solumedrol 500 mg intravenously for three doses. The patient received TMP-SMX for 6 months after transplant.

The patient presented to our institution with a 1-month history of dry cough and dyspnea. A 7-day course of levofloxacin had not led to improvement. There were no fevers, chills, or hemoptysis. A review of her other systems was unremarkable. Physical examination was significant for coarse crackles in both lung bases. A computed tomography (CT) scan of the chest without contrast revealed bilateral interstitial opacities.

At the time of presentation, the patient was receiving mycophenolate mofetil (MMF) 750 mg po bid, tacrolimus 10 mg po bid, and prednisone 80 mg po daily.

The patient was admitted to the hospital and respiratory failure developed. Intubation and mechanical ventilation was required. She was treated with vancomycin, piperacillin–tazobactam, micafungin, and intravenous TMP-SMX 20 mg/kg/day in four divided doses. High doses of corticosteroids were administered. Bronchoalveolar fluid collected by flexible transbronchial bronchoscopy demonstrated PCP on silver methenamine stain. MMF was discontinued. She had

P. Malhotra (✉) · S. D. Rai · D. Hirschwerk
Department of Medicine, Division of Infectious Diseases,
Hofstra North Shore LIJ School of Medicine,
400 Community Drive, Manhasset, NY 11030, USA
e-mail: pmalhotr@nshs.edu

a prolonged hospital course and ultimately died after the family withdrew care.

Our second patient was a 53-year-old African American woman who underwent cadaveric kidney transplantation 13 months prior to presentation. She had a history of diabetes and hypertension. At the time of transplantation, the patient received basiliximab. Acute rejection was diagnosed 10 days after transplantation and she was treated with ATG. PCP prophylaxis with TMP-SMX was maintained for 6 months after transplantation.

The patient presented to our institution with headache and dizziness, accompanied by slurred speech and difficulty ambulating. There were no fevers, seizures, shortness of breath, or cough. She was on MMF 720 mg po bid and tacrolimus 4 mg po bid.

On physical examination, she was noted to be lethargic but arousable. Her pupils were 3 mm symmetrically and reactive to light. Extraocular movements were intact. There was asymmetry of the right side of the face and impaired swallowing. Evaluation of the motor system demonstrated 3/5 strength in each of her lower extremities. Her laboratory examination revealed a white blood cell (WBC) count of 9.2 k/μL with 62 % neutrophils and 13 % lymphocytes, and her creatinine level was 1.2 mg/dL. A brain magnetic resonance imaging (MRI) revealed several ring-enhancing masses with surrounding vasogenic edema. Toxoplasma IgG antibodies were >300 IU/ml in the year prior to transplantation. The results of a brain biopsy of one of these CNS lesions demonstrated *Toxoplasma gondii* microorganisms. The patient was treated with leucovorin, pyrimethamine, and sulfadiazine.

Although the patient's condition stabilized, she remained debilitated.

The incidence of PCP is greatest in the first year after SOT. The incidence is eight times higher in the first year compared to subsequent years. A large number (64 %) of patients at the time of PCP diagnosis had histological evidence of acute or chronic rejection. PCP may continue to occur beyond the first few months after kidney transplantation; the median time to the development of PCP after transplant is 0.8–0.95 years [5]. TMP-SMX prophylaxis has been shown to be extremely effective at preventing PCP and is generally well tolerated [6]. The use of TMP-SMX has also been shown to decrease the incidence of urinary tract and bloodstream infections in transplant recipients, while not altering the number of resistant organisms or microflora [7, 8].

Several recent publications have documented clusters of renal transplant patients with PCP diagnosed after the cessation of prophylaxis. In these studies, graft rejection and use of mammalian target of rapamycin (mTOR) inhibitors was correlated with PCP infection [5]. Recent data from a Japanese center where the incidence of PCP previously had been low and prophylaxis was no longer being given demonstrated an outbreak of 33 cases where molecular analysis was able to demonstrate possible human-to-human transmission [9].

The risk of PCP has been shown to correlate with the number of rejection episodes [10]. Additionally, an association between CMV infection and PCP has been described. Prolongation of PCP prophylaxis in patients with CMV infection has been suggested [3, 10]. A recent study evaluated the association of graft rejection, duration of steroid use, use of mTOR inhibitors, and lymphocytopenia at the time of prophylaxis discontinuation as risk factors for PCP. In the multivariate analysis, only graft rejection [odds ratio (OR) 8.66, $p = 0.017$] remained significantly associated with PCP. It was recommended that, in patients with a history of graft rejection, PCP prophylaxis should be maintained, especially among those with lymphocytopenia [11].

Most toxoplasmosis infections in SOT recipients result from primary infection, with the highest risk occurring in heart transplants. Reactivation of latent toxoplasmosis in kidney transplant recipients is a rare event but may be underreported [12].

Martina et al., in a recent systemic review of the literature, described a total of 42 kidney transplant recipients with toxoplasmosis post-transplantation; half of these cases were thought to be primary. They concluded that the recommended 6 months of prophylaxis with TMP-SMX may delay but not prevent the onset of infection in this population [13].

The current literature supports *Toxoplasma* prophylaxis in serologically mismatched patients, i.e., D+/R−, and is limited to a period of several months after transplantation. No specific prophylaxis for low-risk patients is recommended. Also, prophylaxis of toxoplasmosis in specific populations of SOT recipients receiving T-lymphocyte-depleting antibodies has not been addressed.

Presently, T-lymphocyte-depleting antibodies are a common part of induction therapy. They have been shown to cause T cell depletion, induction of apoptosis of B cell lineages, and interference with dendritic cells, regulatory T cells, and natural killer cell function [14]. They also reduce the number of acute rejection episodes after kidney transplantation [15].

However, these therapies have been shown to cause increased viral activation, particularly of CMV and Epstein–Barr virus (EBV) [16, 17]. Use of these agents is also associated with infections with JC polyoma and other viruses, as well as fungal infections, after prophylaxis has been discontinued. Prolongation of prophylaxis in patients receiving ATG to 6–12 months has been recommended [18, 19].

In conclusion, certain transplant recipients, including patients who have received anti-lymphocyte therapies or

who have undergone treatment for acute rejection episodes, are at higher risk of developing opportunistic infections, including PCP and toxoplasmosis. Based on our experience, we currently recommend lifelong TMP-SMX, as tolerated at our center in renal transplant recipients. Of course, the prolongation of prophylaxis and its benefits need to be weighed against the potential adverse effects of prolonged antibiotics exposure. Further studies to examine this issue should be undertaken.

Conflict of interest None.

References

1. Fishman JA. Infection in solid-organ transplant recipients. N Engl J Med. 2007;357:2601–14.
2. Fishman JA. Prevention of infection caused by *Pneumocystis carinii* in transplant recipients. Clin Infect Dis. 2001;33: 1397–405.
3. Martin SI, Fishman JA; AST Infectious Diseases Community of Practice. Pneumocystis pneumonia in solid organ transplant recipients. Am J Transplant. 2009;9:S227–33.
4. Orr KE, Gould FK, Short G, et al. Outcome of *Toxoplasma gondii* mismatches in heart transplant recipients over a period of 8 years. J Infect. 1994;29:249–53.
5. Neff RT, Jindal RM, Yoo DY, Hurst FP, Agodoa LY, Abbott KC. Analysis of USRDS: incidence and risk factors for *Pneumocystis jiroveci* pneumonia. Transplantation. 2009;88:135–41.
6. Di Cocco P, Orlando G, Bonanni L, et al. A systematic review of two different trimetoprim–sulfamethoxazole regimens used to prevent *Pneumocystis jirovecii* and no prophylaxis at all in transplant recipients: appraising the evidence. Transplant Proc. 2009;41:1201–3.
7. Rubin RH. Infection in the organ transplant recipient. In: Rubin RH, Young LS, editors. Clinical approach to infection in the compromised host. 3rd ed. New York: Plenum Publishing; 1994. p. 629–705.
8. Fox BC, Sollinger HW, Belzer FO, Maki DG. A prospective, randomized, double-blind study of trimethoprim–sulfamethoxazole for prophylaxis of infection in renal transplantation: clinical efficacy, absorption of trimethoprim–sulfamethoxazole, effects on the microflora, and the cost–benefit of prophylaxis. Am J Med. 1990;89:255–74.
9. Yazaki H, Goto N, Uchida K, Kobayashi T, Gatanaga H, Oka S. Outbreak of *Pneumocystis jiroveci* pneumonia in renal transplant recipients: *P. jiroveci* is contagious to the susceptible host. Transplantation. 2009;88:380–5.
10. Arend SM, Westendorp RG, Kroon FP, et al. Rejection treatment and cytomegalovirus infection as risk factors for *Pneumocystis carinii* pneumonia in renal transplant recipients. Clin Infect Dis. 1996;22:920–5.
11. De Castro N, Xu F, Porcher R, Pavie J, Molina JM, Peraldi MN. *Pneumocystis jirovecii* pneumonia in renal transplant recipients occurring after discontinuation of prophylaxis: a case–control study. Clin Microbiol Infect. 2010;16:1375–7.
12. Derouin F, Pelloux H; ESCMID Study Group on Clinical Parasitology. Prevention of toxoplasmosis in transplant patients. Clin Microbiol Infect. 2008;14:1089–101.
13. Martina MN, Cervera C, Esforzado N, et al. *Toxoplasma gondii* primary infection in renal transplant recipients. Two case reports and literature review. Transpl Int. 2011;24:e6–12.
14. Mohty M. Mechanisms of action of antithymocyte globulin: T-cell depletion and beyond. Leukemia. 2007;21:1387–94.
15. Schwartz JJ, Ishitani MB, Weckwerth J, Morgenstern B, Milliner D, Stegall MD. Decreased incidence of acute rejection in adolescent kidney transplant recipients using antithymocyte induction and triple immunosuppression. Transplantation. 2007;84: 715–21.
16. Schooley RT, Hirsch MS, Colvin RB, et al. Association of herpesvirus infections with T-lymphocyte-subset alterations, glomerulopathy, and opportunistic infections after renal transplantation. N Engl J Med. 1983;308:307–13.
17. Cheeseman SH, Henle W, Rubin RH, et al. Epstein–Barr virus infection in renal transplant recipients. Effects of antithymocyte globulin and interferon. Ann Intern Med. 1980;93:39–42.
18. Issa NC, Fishman JA. Infectious complications of antilymphocyte therapies in solid organ transplantation. Clin Infect Dis. 2009;48: 772–86.
19. Louis S, Audrain M, Cantarovich D, et al. Long-term cell monitoring of kidney recipients after an antilymphocyte globulin induction with and without steroids. Transplantation. 2007;83: 712–21.