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Original Article

Efficacies of atovaquone, pentamidine, and trimethoprim/sulfamethoxazole for the prevention of *Pneumocystis jirovecii* pneumonia in patients with connective tissue diseases☆

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ABSTRACT

Background: *Pneumocystis jirovecii* pneumonia (PCP) is an opportunistic infection in patients on steroid therapy for connective tissue diseases. The standard agent for primary PCP prophylaxis is trimethoprim/sulfamethoxazole (TMP-SMX), although this agent can cause common adverse reactions, including myelosuppression and renal toxicity, that result in cessation. Aerosolized pentamidine and oral atovaquone are alternatives for PCP prophylaxis. The efficacies of atovaquone, pentamidine, and TMP-SMX to prevent PCP in patients with connective tissue diseases have never been compared.

Methods: Hospitalized patients with connective tissue diseases who started steroid therapy and PCP prophylaxis were enrolled. PCP prophylaxis regimens were oral TMP-SMX, aerosolized pentamidine, or oral atovaquone. Information was retrospectively collected from medical records about laboratory findings, duration of PCP prophylaxis, and reasons for terminating PCP prophylaxis.

Results: Ninety-six patients received PCP prophylaxis. All of them were initially treated with TMP-SMX, but this was replaced during the study period with pentamidine in 33 patients and with atovaquone in 7. Forty-one (43%) patients discontinued TMP-SMX because of adverse events, and 5 (15%) also discontinued pentamidine. None of the patients discontinued atovaquone. The most frequent causes of TMP-SMX and pentamidine cessation were cytopenia (N = 15) and asthma (N = 2). The rates of continuing treatment with TMP-SMX, pentamidine, and atovaquone at one year after starting PCP prophylaxis were 55.3%, 68.6%, and 100%, respectively (P = 0.01). None of the patients developed PCP.

Conclusion: Although TMP-SMX for PCP prophylaxis had to be discontinued in 43% of patients with connective tissue diseases, pentamidine and atovaquone were well tolerated.

1. Introduction

Pneumocystis jirovecii pneumonia (PCP) is a frequent opportunistic infection in immunocompromised patients, such as those with HIV infection. The guidelines for primary PCP prophylaxis of patients infected with HIV in the USA recommend trimethoprim-sulfamethoxazole (TMP-SMX) [1]. However, common adverse events, including skin rash, myelosuppression, nausea, fever, and renal and liver toxicities, can result in withdrawal of TMP-SMX therapy [2]. Aerosolized pentamidine and oral atovaquone are alternatives for PCP prophylaxis.

Immunosuppressive agents and high-dose steroids are used to treat connective tissue diseases including rheumatoid arthritis and systemic lupus erythematosus. These drugs induce cellular immune dysfunction in patients with connective tissue diseases, HIV infection, and hematological and nonhematological transplantation. Notably, in patients with connective tissue diseases, TMP-SMX has been shown to have preventive effects compared to no prophylactic treatment [3], and it is generally the first choice in the clinical setting, although it is often replaced with an alternative due to adverse effects. However, the effectiveness of PCP prophylactic agents against connective tissue diseases and whether they can be safely and continuously administered remain unknown. The

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present study aimed to determine patient tolerance and the effectiveness of PCP prophylactic agents in patients with connective tissue diseases.

2. Patients and methods

2.1. Patients

Adult hospitalized patients who had started steroid therapy and PCP prophylaxis for connective tissue diseases between October 2014 and October 2016 at Teikyo University Hospital, which is a teaching hospital in Tokyo, were enrolled. Patients with a history of allergies to the prophylactic drugs were excluded. The institutional review board of our hospital approved our review of the infection control data. The need for informed consent was waived due to the retrospective nature of the study.

2.2. Definitions

Stopping prophylaxis due to suspected toxicity of the studied agents and requiring alternative prophylactic medications was considered a prophylaxis-limiting adverse effect. Completing prophylaxis free of adverse reactions was defined as stable clinical and respiratory status sustained during the administration of the PCP prophylactic drug and at least four weeks after the PCP prophylactic drug was stopped. The diagnosis of PCP was confirmed by finding pneumocystis organisms in respiratory specimens.

2.3. Medication, dosage, and duration of PCP prophylaxis

The PCP prophylactic regimens were oral TMP 80 mg with oral SMX 400 mg per day, aerosolized pentamidine 300 mg per month, or oral atovaquone suspension 1500 mg per day. Prophylaxis was stopped when the daily dose of steroid or other immunosuppressants was tapered according to the decision of the attending physician.

2.4. Data collection

Medical laboratory data, durations of steroid therapy and PCP prophylaxis, and reasons for PCP prophylaxis termination were collected from medical records.

2.5. Statistical analysis

Categorical and continuous variables were analyzed using Fisher's exact test and Student's *t*-test, respectively. The amount of time continuing PCP prophylaxis was analyzed using Kaplan-Meier curves, which were compared using log-rank tests. All tests were two-sided, with a P value < 0.05 considered significant. Data were statistically analyzed using PASW Statistics software, version 17.0.2 (WinWrap® Basic).

3. Results

3.1. Patients and continuation of PCP prophylactic drugs

Table 1 summarizes the baseline clinical and demographic characteristics of the 96 patients with connective tissue diseases who received PCP prophylaxis. No patient had a history of allergy to PCP prophylactic drugs before the start of treatment.

All patients were initially treated with TMP-SMX, but 41 (43%) of them could not continue on this agent during the study period because of adverse events (Table 2). Pentamidine and atovaquone were given to 33 and 2 patients, respectively, as alternatives. However, 5 (15%) of the 33 patients also had to discontinue pentamidine. Both patients on atovaquone were able to continue the course of administration. None of the patients who discontinued any PCP prophylactic agent were given it again. There were 41 patients who completed PCP prophylaxis by tapering the daily dose of steroids, but no patients completed PCP prophylaxis by tapering or stopping other immunosuppressants. None of the patients developed PCP during prophylaxis.

The rates at which prophylactic agents were continued at one year after starting PCP prophylaxis were 55.3%, 68.6%, and 100% for TMP-SMX, pentamidine, and atovaquone, respectively ($P = 0.01$; Fig. 1).

Table 1
Clinical factors of patients with collagen diseases who started prophylaxis for *Pneumocystis jirovecii* pneumonia.

Clinical factor	Patients (N = 96)
Median age (y; range)	66.5 (17–90)
Males:Females	21:75
Underlying collagen disease	
Systemic lupus erythematosus	21
Polymyositis/Dermatomyositis	12
Rheumatoid arthritis	10
Microscopic polyangiitis	6
Adult onset Still disease	6
Immunoglobulin G4-related diseases	4
Mixed connective tissue disease	3
Eosinophilic granulomatosis with polyangiitis	3
Other	12

Table 2
Selection of prophylactic agents against *Pneumocystis jirovecii* pneumonia.

	TMP-SMX	Pentamidine	Atovaquone
Initial agent	96	0	0
Discontinuation	41	5	0
TMP-SMX replacement	–	33	2
Pentamidine replacement	0	–	5
Final selection of agents	55	28	7
Completion of prophylaxis	21	20	0
Development of PCP	0	0	0

PCP, *Pneumocystis jirovecii* pneumonia; TMP-SMX, trimethoprim/sulfamethoxazole.

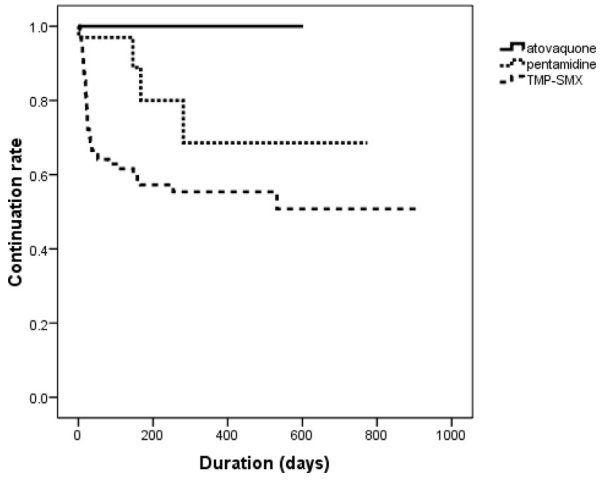

Fig. 1. Kaplan-Meier curves of continuation rates relative to numbers of days on PCP prophylactic agents. TMP-SMX, trimethoprim/sulfamethoxazole.

3.2. Reasons for stopping PCP prophylaxis

The adverse events of cytopenia (N = 15) and asthma (N = 2) were the most frequent reasons for stopping prophylaxis with TMP-SMX and pentamidine, respectively (Table 3).

Platelet counts, estimated glomerular filtration rate (eGFR), and serum creatinine levels before prophylaxis were compared between patients who stopped and those who continued/completed the TMP-SMX regimen (Table 4). Platelet counts and eGFR tended to be lower and creatinine levels tended to be higher in the patients who stopped taking TMP-SMX, but the differences were not significant.

Table 4
Comparison of platelet counts, estimated glomerular filtration rate, and serum creatine levels before prophylaxis in patients who completed or stopped therapy with TMP-SMX.

	Stopped (N = 41)	Continued/Completed (N = 55)	p
Platelets ($\times 10^4/\mu L$)	23.8 ± 14.1	28.8 ± 10.2	0.067
eGFR (mL/min/1.73 m^2)	73.0 ± 24.0	76.8 ± 28.0	0.242
Serum creatinine (mg/dL)	0.83 ± 0.60	0.73 ± 0.20	0.191

Values are shown as means ± standard deviation. TMP-SMX, trimethoprim/sulfamethoxazole; eGFR, estimated glomerular filtration rate.

4. Discussion

Pneumocystis jirovecii is a pathogen of opportunistic infections in immunocompromised hosts, such as those who are administered corticosteroids. None of the patients who were administered prophylactic agents in the present study developed PCP. According to a retrospective study at the National Institutes of Health, 6% of patients with PCP with granulomatosis and polyangiitis did not receive PCP prophylaxis [3]. One review that analyzed the outcomes of 11 trials found that only granulomatosis with polyangiitis among collagen vascular diseases was associated with PCP rates >2.5% [4]. That review found much lower rates of PCP among other pathologies examined, including systemic lupus erythematosus and rheumatoid arthritis, in patients on immunosuppressive therapy with corticosteroids or cytotoxic agents [4]. The reported incidence of PCP in rheumatoid arthritis is 0.17/100 person-years [5]. Previous studies have indicated that prophylaxis with TMP-SMX leads to the prevention of PCP in patients with connective tissue diseases [6–9]. We considered that the absence of PCP in the present study was due to the preventive effects of prophylactic drugs.

The present study found that TMP-SMX, pentamidine, and atovaquone conferred effective prophylaxis against PCP in patients with connective tissue diseases. This is the first study to compare the effects of these three prophylactic agents on PCP and the safety of these agents in patients with connective tissue diseases. A comparison of the effects of TMP-SMX, dapsone, and pentamidine on the incidence of PCP in HIV-infected patients found a lower rate of PCP in patients on TMP-SMX than on other agents [10]. One study found that both full-dose atovaquone and TMP-SMX prevented PCP in 185 patients with renal transplantation [11]. Atovaquone was less effective than TMP-SMX in a trial of patients with AIDS [12]. However, the efficacies of atovaquone and TMP-SMX to prevent PCP in patients with connective tissue diseases have not been compared until now. We considered that pentamidine and atovaquone could be effective alternatives to TMP-SMX for PCP prophylaxis in patients with connective tissue diseases.

Table 3
Reasons for discontinuing prophylaxis for *Pneumocystis jirovecii* pneumonia.

Reasons for discontinuation	TMP-SMX (N = 41)	Pentamidine (N = 5)
Cytopenia	15	0
Creatinine elevation	6[a]	0
Electrolyte abnormalities	5[a]	0
Hyperkalemia	3[b]	0
Hyponatremia	3[b]	0
Skin rash	6	0
Asthma	0	2
Other/unknown	10	3

TMP-SMX, trimethoprim/sulfamethoxazole. Reasons for discontinuation were judged from medical records or medical laboratory data.
[a] In one case, TMP-SMX discontinued for both reasons.
[b] In one case, TMP-SMX discontinued for both abnormalities.

Some patients develop adverse reactions to TMP-SMX. Park et al. reported that the incidence of adverse events associated with TMP-SMX was 21.2/100 person-years for patients with rheumatic arthritis treated with high-dose steroids [9]. Carr et al. found no significant difference in the rate of adverse reactions between TMP-SMX and aerosolized pentamidine as secondary prophylaxis against PCP in patients with AIDS [13]. A prospective comparison of atovaquone and TMP-SMX for PCP prophylaxis following autologous peripheral blood stem cell transplantation found a lower rate of intolerance to atovaquone than to TMP-SMX [14]. Another comparison of atovaquone with TMP-SMX for PCP prophylaxis after renal transplantation found that the need for dose reduction and premature cessation of therapy secondary to adverse events was more prevalent among patients treated with TMP-SMX [11]. These and the present findings indicate that pentamidine and atovaquone were well tolerated by patients with connective tissue diseases who could not tolerate TMP-SMX.

No consensus about PCP prophylaxis for patients with connective tissue diseases has been reached. The European Conference on Infections in Leukaemia guidelines recommend aerosolized pentamidine, dapsone, and atovaquone as second-line options for patients who must discontinue TMP-SMX prophylaxis [15]. The final choice might depend on agent-specific characteristics, including the route and frequency of administration, marrow toxicity, additional prophylactic coverage, availability, specific toxicities, and cost.

The rate of TMP-SMX discontinuation within 30 days after starting PCP prophylaxis was high in the present study. A previous study of primary PCP prophylaxis for patients with HIV found that the mean number of days to the onset of adverse reactions in patients treated with 480 and 960 mg of TMP-SMX, respectively, was 57 (range, 7 to 191) vs. 16 (range, 5 to 35) days (P = 0.02) [16]. Adverse events might be a result of dose-related cumulative toxicity caused by the accumulation of reactive metabolites of sulfamethoxazole rather than of hypersensitivity [17]. Thrombocytopenia due to TMP-SMX is induced by an antibody-mediated immune mechanism [18]. Acute interstitial nephritis induced by TMP-SMX might be associated with hypersensitivity reactions [19]. However, an association between the mechanisms of adverse reactions to TMP-SMX and the backgrounds of connective tissue diseases has not been clarified. Avoiding agents with a high likelihood of eliciting adverse reactions would be better than increasing glucocorticoid doses for the long-term management of connective tissue diseases. Therefore, we suggest that careful observation is necessary in the early stage of PCP prophylaxis, and that any agent that causes adverse effects should be withdrawn immediately.

The present study found that baseline platelet counts, eGFR, and serum creatinine values before starting prophylaxis for PCP were not associated with thrombocytopenia and creatinine elevation in

patients given TMP-SMX. In a retrospective cohort study of predictors for cutaneous hypersensitivity reactions to TMP-SMX in the setting of primary PCP prophylaxis, clinical and laboratory variables were apparently not sufficiently closely associated with the reactions as to permit the development of a useful prediction rule [20]. Although not significantly associated with TMP-SMX discontinuation, we suggest that patients with low platelet counts and high serum creatinine values should be very carefully monitored.

This study has the following limitations. The retrospective nature of the investigation, the single-center analysis, and the small patient cohort led to unbalanced baseline characteristics with respect to the administration of the different prophylactic agents. A precise risk-benefit assessment of patients with connective tissue diseases could not be performed because PCP did not occur. TMP-SMX is known to increase the creatinine value independently of renal function, because TMP inhibits tubular creatinine secretion [21]. Among the patients whose reason for TMP-SMX discontinuation was due to creatinine increase or eGFR decrease, patients who did not develop true renal dysfunction might be included. In a study of adverse renal effects of TMP-SMX, however, of 573 patients who received treatment with TMP-SMX, 28 (4.9%) developed acute kidney injury according to Acute Injury Network criteria, and one patient required dialysis [22]. Neither dose nor duration was an independent risk factor. Additional prospective research using multiple biomarkers of renal dysfunction will be required to determine the safety of TMP-SMX.

In conclusion, 43% of patients with connective tissue diseases discontinued TMP-SMX for prophylaxis against PCP. Patients with connective tissue diseases who were unable to tolerate TMP-SMX for PCP prophylaxis were able to tolerate pentamidine and atovaquone well.

Conflicts of interest

None.

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References

[1] Masur H, Brooks JT, Benson CA, Holmes KK, Pau AK, Kaplan JE. Prevention and treatment of opportunistic infections in hiv-infected adults and adolescents: updated guidelines from the centers for disease control and prevention, national institutes of health, and hiv medicine association of the infectious diseases society of America. Clin Infect Dis 2014;58:1308–11. http://doi.org.10.1093/cid/ciu094.

[2] Smilack JD. Trimethoprim-sulfamethoxazole. Mayo Clin Proc 1999;74:730–4. http://doi.org.https://doi.org/10.4065/74.7.730.

[3] Ognibene FP, Shelhamer JH, Hoffman GS, Kerr GS, Reda D, Fauci AS, et al. Pneumocystis carinii pneumonia: a major complication of immunosuppressive therapy in patients with wegener's granulomatosis. Am J Respir Crit Care Med 1995;151:795–9. http://doi.org.10.1164/ajrccm/151.3_Pt_1.795.

[4] Green H, Paul M, Vidal L, Leibovici L. Prophylaxis for pneumocystis pneumonia (pcp) in non-hiv immunocompromised patients. Cochrane Database Syst Rev 2007. https://doi.org/10.1002/14651858.CD005590.pub2:CD005590. http://doi.org.10.1002/14651858.CD005590.pub2.

[5] Hashimoto A, Suto S, Horie K, Fukuda H, Nogi S, Iwata K, et al. Incidence and risk factors for infections requiring hospitalization, including pneumocystis pneumonia, in Japanese patients with rheumatoid arthritis. Int J Rheumatol 2017;2017:6730812. http://doi.org.10.1155/2017/6730812.

[6] Vananuvat P, Suwannalai P, Sungkanuparph S, Limsuwan T, Ngamjanyaporn P, Janwityanujit S. Primary prophylaxis for pneumocystis jirovecii pneumonia in patients with connective tissue diseases. Semin Arthritis Rheum 2011;41:497–502. http://doi.org.10.1016/j.semarthrit.2011.05.004.

[7] Okada J, Kadoya A, Rana M, Ishikawa A, Iikuni Y, Kondo H. Efficacy of sulfamethoxazole-trimethoprim administration in the prevention of pneumocystis carinii pneumonia in patients with connective tissue disease. Kansenshogaku Zasshi 1999;73:1123–9.

[8] Kimura M, Tanaka S, Ishikawa A, Endo H, Hirohata S, Kondo H. Comparison of trimethoprim–sulfamethoxazole and aerosolized pentamidine for primary prophylaxis of pneumocystis jiroveci pneumonia in immunocompromised patients with connective tissue disease. Rheumatol Int 2008;28:673–6. http://doi.org.10.1007/s00296-007-0505-4.

[9] Park JW, Curtis JR, Moon J, Song YW, Kim S, Lee EB. Prophylactic effect of trimethoprim-sulfamethoxazole for pneumocystis pneumonia in patients with rheumatic diseases exposed to prolonged high-dose glucocorticoids. Ann Rheum Dis 2018;77:644–9. http://doi.org.10.1136/annrheumdis-2017-211796.

[10] Warnock AC, Rimland D. Comparison of trimethoprim-sulfamethoxazole, dapsone, and pentamidine in the prophylaxis of pneumocystis carinii pneumonia. Pharmacotherapy 1996;16:1030–8.

[11] Gabardi S, Millen P, Hurwitz S, Martin S, Roberts K, Chandraker A. Atovaquone versus trimethoprim-sulfamethoxazole as pneumocystis jirovecii pneumonia prophylaxis following renal transplantation. Clin Transplant 2012;26:E184–90. http://doi.org.10.1111/j.1399-0012.2012.01624.x.

[12] Hughes W, Leoung G, Kramer F, Bozzette SA, Safrin S, Frame P, et al. Comparison of atovaquone (566c80) with trimethoprim-sulfamethoxazole to treat pneumocystis carinii pneumonia in patients with aids. N Engl J Med 1993;328:1521–7. http://doi.org.10.1056/NEJM199305273282103.

[13] Carr A, Tindall B, Penny R, Cooper DA. Trimethoprim-sulphamethoxazole appears more effective than aerosolized pentamidine as secondary prophylaxis against pneumocystis carinii pneumonia in patients with aids. AIDS 1992;6:165–71.

[14] Colby C, McAfee S, Sackstein R, Finkelstein D, Fishman J, Spitzer T. A prospective randomized trial comparing the toxicity and safety of atovaquone with trimethoprim/sulfamethoxazole as pneumocystis carinii pneumonia prophylaxis following autologous peripheral blood stem cell transplantation. Bone Marrow Transplant 1999;24:897–902. http://doi.org.10.1038/sj.bmt.1702004.

[15] Maertens J, Cesaro S, Maschmeyer G, Einsele H, Donnelly JP, Alanio A, et al. Ecil guidelines for preventing pneumocystis jirovecii pneumonia in patients with haematological malignancies and stem cell transplant recipients. J Antimicrob Chemother 2016;71:2397–404. http://doi.org.10.1093/jac/dkw157.

[16] Schneider MM, Hoepelman AI, Eeftinck Schattenkerk JK, Nielsen TL, van der Graaf Y, Frissen JP, et al. A controlled trial of aerosolized pentamidine or trimethoprim-sulfamethoxazole as primary prophylaxis against pneumocystis carinii pneumonia in patients with human immunodeficiency virus infection. The Dutch aids treatment group. N Engl J Med 1992;327:1836–41. http://doi.org.10.1056/NEJM199212243272603.

[17] van der Ven AJ, Koopmans PP, Vree TB, van der Meer JW. Adverse reactions to co-trimoxazole in hiv infection. Lancet 1991;338:431–3.

[18] Kiefel V, Santoso S, Schmidt S, Salama A, Mueller-Eckhardt C. Metabolite-specific (igg) and drug-specific antibodies (igg, igm) in two cases of trimethoprim-sulfamethoxazole-induced immune thrombocytopenia. Transfusion 1987;27:262–5.

[19] Smith EJ, Light JA, Filo RS, Yum M. Interstitial nephritis caused by trimethoprim-sulfamethoxazole in renal transplant recipients. J Am Med Assoc 1980;244:360–1. http://doi.org.10.1001/jama.1980.03310040042025.

[20] Hennessy S, Strom BL, Berlin JA, Brennan PJ. Predicting cutaneous hypersensitivity reactions to cotrimoxazole in hiv-infected individuals receiving primary pneumocystis carinii pneumonia prophylaxis. J Gen Intern Med 1995;10:380–6.

[21] Delanaye P, Mariat C, Cavalier E, Maillard N, Krzesinski JM, White CA. Trimethoprim, creatinine and creatinine-based equations. Nephron Clin Pract 2011;119:c187–93. Discussion c93-4, http://doi.org.10.1159/000328911.

[22] Fraser TN, Avellaneda AA, Graviss EA, Musher DM. Acute kidney injury associated with trimethoprim/sulfamethoxazole. J Antimicrob Chemother 2012;67:1271–7. http://doi.org.10.1093/jac/dks030.