Evaluation of the corticosteroid dose at Pneumocystis pneumonia onset in non-HIV patients receiving steroids and the period from the discontinuation of trimethoprim-sulfamethoxazole prophylaxis to the onset of Pneumocystis pneumonia

Daiki Inoue (✉ d-inoue@kitano-hp.or.jp)

Kitano Hospital

Hirotaka Tamesada

Kitano Hospital

Tomoki Maetani

Kitano Hospital

Sho Yamada

Kitano Hospital

Yujiro Kikuchi

Kitano Hospital

Michihiro Uyama

Kitano Hospital

Yusuke Hayashi

Kitano Hospital

Takamitsu Imoto

Kitano Hospital

Yoko Hamakawa

Kitano Hospital

Takamasa Kitajima

Kitano Hospital

Satoshi Marumo

Kitano Hospital

Motonari Fukui

Kitano Hospital

Research Article

Abstract

Background

Pneumocystis pneumonia (PCP) is a life-threatening opportunistic infection among non-human immunodeficiency virus (non-HIV) immunocompromised patients. The prophylactic use of trimethoprim-sulfamethoxazole (TMP-SMX) reduces PCP incidence. However, it remains unclear when TMP-SMX can be safely discontinued among patients for whom corticosteroid tapering is underway, and occasionally, PCP develops after TMP-SMX discontinuation despite tapering of corticosteroids to considerably lower dose.

Methods

We retrospectively reviewed non-HIV immunocompromised patients who were diagnosed with PCP in our institution during a 12-year period (January 2007 to December 2018). We analysed the clinical information including corticosteroid doses when PCP developed and the period from TMP-SMX discontinuation to PCP onset for these patients.

Results

In all, 39 patients were included. The median patient age was 70 years (range: 27–92 years), and 18 patients (46.2%) were female. Thirty-two patients (82.1%) were administered corticosteroids. The median daily corticosteroid dose converted to the prednisolone equivalent dose was 14 mg (range: 2–60 mg). Further, six (15.4%) patients were treated with a dose of 5 mg or less. Twenty-eight patients (71.8%) were never administered TMP-SMX, and TMP-SMX was discontinued before PCP development in the remaining 11 patients. The median period from TMP-SMX discontinuation to PCP development was 95 days (range: 44–175 days), and in nine patients, PCP developed 14 ± 2 weeks after TMP-SMX discontinuation.

Conclusions

PCP developed in non-HIV patients treated with corticosteroids at doses considerably lower than the daily 20 mg prednisolone equivalent dose. Non-HIV immunocompromised patients are more likely to develop PCP approximately 3 months after TMP-SMX discontinuation.

Background

Pneumocystis pneumonia (PCP), which is caused by *Pneumocystis jirovecii*, is a common opportunistic infection among human immunodeficiency virus (HIV)-positive patients as well as HIV-negative (non-HIV) immunocompromised patients with hematologic malignancies; solid and bone marrow transplant

recipients; and patients administered with immunosuppressive therapies such as corticosteroids, biological drugs, or anticancer drugs. The mortality rate in HIV-positive patients with PCP has declined to 10–20%; however, among non-HIV patients, PCP is life-threatening and the mortality rate remains 30–60% [1].

The use of prophylactic drugs can reduce the incidence of PCP in both HIV patients and non-HIV immunocompromised patients. Although primary prophylactic treatment for PCP is considered in HIV patients with CD4 cell counts of < 200 cells/mm, the treatment has been controversial in non-HIV immunocompromised patients [2–4]. Yale and Limper [5] suggested that primary prophylaxis should be considered for patients receiving corticosteroid therapy equivalent to at least 20 mg of prednisolone (PSL) daily for more than 4 weeks in non-HIV patients. However, we have experienced several cases in which PCP developed after the discontinuation of primary prophylaxis despite tapering of corticosteroids to lower than the daily 20 mg PSL equivalent dose. It is necessary to establish a consensus about when prophylaxis treatment against PCP should be started and when it can be safely stopped in non-HIV immunocompromised patients for whom corticosteroid therapy is being tapered.

Trimethoprim-sulfamethoxazole (TMP-SMX) is the first choice for prophylactic treatment in HIV patients. The prophylactic effect of TMP-SMX in non-HIV immunocompromised patients has also been reported [6, 7]. However, the prophylactic use of TMP-SMX is known to be associated with many adverse effects, such as hyperkalaemia, pancytopenia, rash, interstitial nephritis, aseptic meningitis, hepatitis, and pancreatitis [8], which often result in its discontinuation. Although aerosolized pentamidine or atovaquone can be used as the second or third choice when TMP-SMX is unavailable [9], these treatments might not be initiated until the improvement of the adverse event caused by the TMP-SMX treatment. Such delays in restarting prophylaxis could lead to the development of PCP. If it is known how long the prophylactic effects of TMP-SMX prevent PCP after treatment discontinuation, the risk of PCP development could be more precisely evaluated in such conditions. In this study, we retrospectively investigated the dose of corticosteroids at the time of PCP development in non-HIV immunocompromised patients. We also evaluated the period from the discontinuation of TMP-SMX prophylaxis to the onset of PCP to elucidate the prolonged prophylactic effect of this treatment.

Methods

Patients

We included non-HIV immunocompromised patients who were diagnosed with PCP from January 2007 to December 2018 in Tazuke Kofukai Medical Research Institute, Kitano Hospital, Osaka, Japan. The study was approved by the ethics committee of Kitano Hospital (approval no. P200501200). The inclusion criteria were as follows: (1) presence of an underlying immunodeficiency known to be associated with PCP; (2) clinical symptoms consistent with a lower respiratory tract infection, e.g., cough and/or dyspnoea; (3) presence of new pulmonary infiltrates on chest radiography; (4) the presence of *P. jirovecii* proven by deoxyribonucleic acid (DNA) detection through polymerase chain reaction (PCR) or a positive

fluorescent staining result for a bronchoalveolar lavage fluid (BALF) or sputum sample; and (5) elevated plasma (1−3)-β-D-glucan (β-D-glucan) levels measured using the Wako β-glucan assay (Fujifilm Wako Chemicals). We excluded patients infected with HIV.

Data collection

Patients' clinical and laboratory data were retrospectively reviewed and collected. These data included age; sex; smoking status; underlying diseases such as autoimmune diseases, malignancies, interstitial pneumonia, diabetes mellitus, and renal diseases; history of renal transplantation; corticosteroid dose and duration; immunosuppressant use; prophylactic TMP-SMX use (if discontinued, the period from discontinuation to the development of PCP); prophylactic aerosolized pentamidine or atovaquone use; initial laboratory findings; diagnostic methods (BALF or sputum); and in-hospital mortality.

Statistical analysis

Categorical variables are described as counts and percentages, and continuous variables as median values and ranges. Fisher's exact test was used to analyse categorical variables, and the Mann−Whitney U test was used to analyse continuous variables to compare two groups. A two-sided P value of less than 0.05 was considered statistically significant. All statistical analyses were performed with the statistical software R (version 3.6.0; R Foundation).

Results

Patient characteristics

In all, 210,414 patients who were hospitalized in our facility during the study period were screened. Of those, 39 patients met all the inclusion criteria (Fig. 1). Fifteen (38.5%) and 23 (59.0%) patients were diagnosed as *P. jirovecii*-positive based on PCR results of BALF and sputum samples, respectively. Fluorescent staining of BALF samples was positive for four patients (10.3%) including one patient with a negative PCR result. The patients' baseline characteristics are shown in Table 1. The median patient age was 70 years (range: 27−92 years), and 18 patients (46.2%) were female. Twenty-one patients (53.8%) had autoimmune diseases and 13 patients (33.3%) had malignancies; seven of the 13 patients had had hematologic malignancies. Thirty-two (82.1%) and 14 (35.9%) patients were being treated with corticosteroids and immunosuppressants, respectively, and among them, 11 (28.2%) received both corticosteroids and immunosuppressants at the time of PCP development. Among the 32 patients who were being treated with corticosteroids, the daily corticosteroid dose converted to the PSL equivalent dose ranged from 2 to 60 mg, with the median dose being 14 mg. Further, 24 (61.5%), 11 (28.2%), and six (15.4%) patients were treated with a dose of 20 mg or less, 10 mg or less, and 5 mg or less, respectively (Fig. 2). The corticosteroid administration period ranged from 27 to 2,084 days, with the median period being 121 days. None of 39 patients was being administered TMP-SMX for prophylaxis when PCP developed. Aerosolized pentamidine was administered to only four patients; in three of the patients, it was administered from the beginning of prophylactic treatment, and in the remaining patient, it was

administered after TMP-SMX discontinuation. The remaining 35 patients were not being administered any prophylactic drug when PCP developed; 25 of these patients never received prophylaxis, while the remaining 10 had discontinued TMP-SMX before PCP development. Seventeen patients (43.6%) died at the hospital.

Comparison of the characteristics of patients who were never administered and those who discontinued the prophylactic TMP-SMX treatment

Twenty-five patients were never administered TMP-SMX as prophylaxis for PCP and 11 other patients discontinued TMP-SMX before PCP development (Table 2). There were no significant differences between the two groups in age, sex, underlying diseases, initial laboratory findings, corticosteroid use or dose, immunosuppressant use, diagnostic methods, and in-hospital mortality. The duration of corticosteroid treatment was significantly longer in the patients who discontinued prophylactic TMP-SMX than in those who were never administered TMP-SMX (542 [range: 0-2084] days vs 64.5 [range: 0-728] days, p < 0.01). This significant difference existed even after excluding patients who were not being administered corticosteroids at the time of PCP development (739 [range: 116–2084] days vs 155 [range: 27–728] days, p < 0.01).

Patients who discontinued prophylactic TMP-SMX

The detailed characteristics of the 11 patients who discontinued prophylactic TMP-SMX before PCP development are shown in Table 3. Only one patient was administered prophylactic aerosolized pentamidine after TMP-SMX discontinuation due to its side effects. A lymphoma patient was never administered corticosteroid therapy, while the remaining 10 patients had been administered corticosteroids for more than 116 days. The daily corticosteroid dose at the time of PCP development, which was converted to the PSL equivalent dose, ranged from 2 to 30 mg, with the median dose was 10 mg. Four patients (36.4%) were administered a dose of 5 mg or less. All of the patients who died at the hospital were administered a dose of 10 mg or higher. The period from TMP-SMX discontinuation to PCP development ranged from 44 to 175 days, with the median duration being 95 days, and in nine patients (81.8%), PCP developed 14 ± 2 weeks after TMP-SMX discontinuation (Table 3 and Fig. 3).

Discussion

In this study, we evaluated the detailed characteristics of 39 non-HIV patients who developed PCP in our hospital. PCP developed in 19 patients (48.7%) treated with a corticosteroid dose lower than the daily 20 mg PSL equivalent dose, which is the threshold for primary prophylaxis as suggested previously [5]. Furthermore, this finding is consistent that reported previously [10–12]. PCP may be attributable to the different immune statuses of patients who had different underlying diseases and were treated with different immunosuppressive drugs, and the heterogeneity might have made it difficult to evaluate the necessity or indication of prophylaxis for PCP [5, 13].

Moreover, there is little evidence-based guidance about the appropriate timing of discontinuing prophylaxis for PCP [5, 14], and Wolfe et al. [15] reported that 52% of infectious disease physicians consider a dose equivalent to a daily dose of 16–20 mg PSL as the criterion for discontinuing prophylaxis. In recent years, however, many patients have been treated with corticosteroids, immunosuppressive drugs, traditional and new anticancer drugs or biological drugs, or combinations of those. These varieties make it difficult to determine when the prophylaxis for PCP can be stopped safely. In our study, among the 10 patients who had been administered corticosteroid therapy and discontinued prophylactic TMP-SMX before the development of PCP (patient no. 2–11 in Table 3), the corticosteroid dose at the time of TMP-SMX discontinuation varied from 0 to 30 mg equivalent of the daily PSL dose. Three of these patients received TMP-SMX until the corticosteroid dose was tapered to less than 5 mg; one patient (patient no. 3 in Table 3) discontinued TMP-SMX after the cessation of corticosteroid therapy. However, corticosteroid therapy at a dose equivalent to a daily PSL dose of 2.5 mg was restarted owing to the recurrence of graft-versus-host disease. Our study indicates that physicians should be vigilant about the cessation of prophylaxis for PCP, even if the prescribed corticosteroid dose itself is low.

In this study, no patient was administered TMP-SMX for prophylaxis when PCP developed. This means that there was no breakthrough infection of PCP in non-HIV patients with TMP-SMX prophylaxis regardless of underlying characteristics during the study period in our hospital. These findings are consistent with previous reports, which show TMP-SMX may inhibit PCP strongly in non-HIV patients [16, 17]. There was no significant difference in the patient background between the patients who were never treated with prophylactic TMP-SMX and those who discontinued prophylactic TMP-SMX, except for the duration of prior steroid administration. The reason for this difference may be the effect of TMP-SMX. It is understandable that the time from steroid administration to PCP development was longer in the group that received prophylaxis because PCP was prevented during the period under prophylaxis.

Eleven patients developed PCP between 44 and 175 days after the discontinuation of prophylactic TMP-SMX, and nine developed the disease approximately 14 weeks after prophylaxis withdrawal (Fig. 3). This suggests that patients have the maximum risk of developing PCP approximately 3 months after the discontinuation of TMP-SMX prophylaxis. Because the half-lives of both TMP and SMX are shorter than 24 h, the pharmacological prophylactic effect against *P. jirovecii* may persist for much shorter than 3 months. Therefore, we consider that the reason for the 3-month period might be the life cycle of *P. jirovecii*. The culture of *P. jirovecii* is difficult and its life cycle, especially in the human body, is still unclear [18]. Therefore, we cannot prove this consideration by experimental science. However, Yale and Limper [5] reported that the median duration of corticosteroid therapy was 12 weeks before the development of PCP in non-HIV patients with various underlying immunosuppressive disorders. In our study, the median period was 88 days (range: 27–728 days) from the initiation of corticosteroid therapy to PCP development in the patients without TMP-SMX prophylaxis (data not shown). These similarities suggest that it is reasonable to consider that approximately 3 months are needed for *P. jirovecii* infection to exacerbate and PCP development after the loss of suppression by host immunity or prophylactic agents. Hence, prophylaxis should be restarted within 3 months after the adverse event-induced early discontinuation of the primary

prophylaxis. Moreover, we could evaluate the possibility of PCP in non-HIV immunocompromised patients with respiratory symptoms by considering the period from discontinuation of TMP-SMX.

Limitation

There are several limitations to our study. First, *P. jirovecii* detection using PCR or fluorescent staining could provide false-positive results. However, the inclusion criteria comprised clinical symptoms, chest radiography findings, and laboratory findings to exclude such false-positive result as much as possible. Second, the present study was a single-centre retrospective study with a small number of cases. However, it might be difficult to conduct prospective studies because of ethical issues or the frequency of PCP development. Third, this study included all non-HIV patients with PCP. Therefore, the results obtained for the overall patient population comprising individuals with various comorbidities may not be applicable in the case of individual diseases.

Conclusions

Our observational study showed that among non-HIV patients, PCP develops under corticosteroid therapy at doses much lower than the daily 20 mg PSL equivalent dose, indicating that clinicians should consider TMP-SMX prophylaxis for PCP even if the dose of corticosteroid administered is low. Furthermore, non-HIV immunocompromised patients are at a higher risk of developing PCP approximately 3 months after the discontinuation of TMP-SMX prophylaxis. To our knowledge, this may be the first report to elucidate the time required for PCP development after the discontinuation of prophylaxis. Further study is warranted to confirm this result.

List Of Abbreviations

PCP: *Pneumocystis* pneumonia

HIV: human immunodeficiency virus

non-HIV: non-human immunodeficiency virus

TMP-SMX: trimethoprim-sulfamethoxazole

PSL: prednisolone

DNA: deoxyribonucleic acid

PCR: polymerase chain reaction

BALF: bronchoalveolar lavage fluid

Declarations

Ethics approval and consent to participate

The present study was approved by the ethics committee of Kitano Hospital (approval no. P200501200). The need for obtaining informed consent from each patient was waived by the same ethics committee due to a retrospective observational nature of this study. The all methods in the present study were carried out in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

DI study design, data collection, analysis and interpretation, manuscript writing, manuscript edition, a major contributor in writing the manuscript. HT, TM, SY, YK, MU, YH, TI, YH, TK, SM data collection. MF data interpretation, manuscript edition. All authors read and approved the final manuscript.

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Tables

Due to technical limitations, the tables are only available as a download in the supplemental files section.
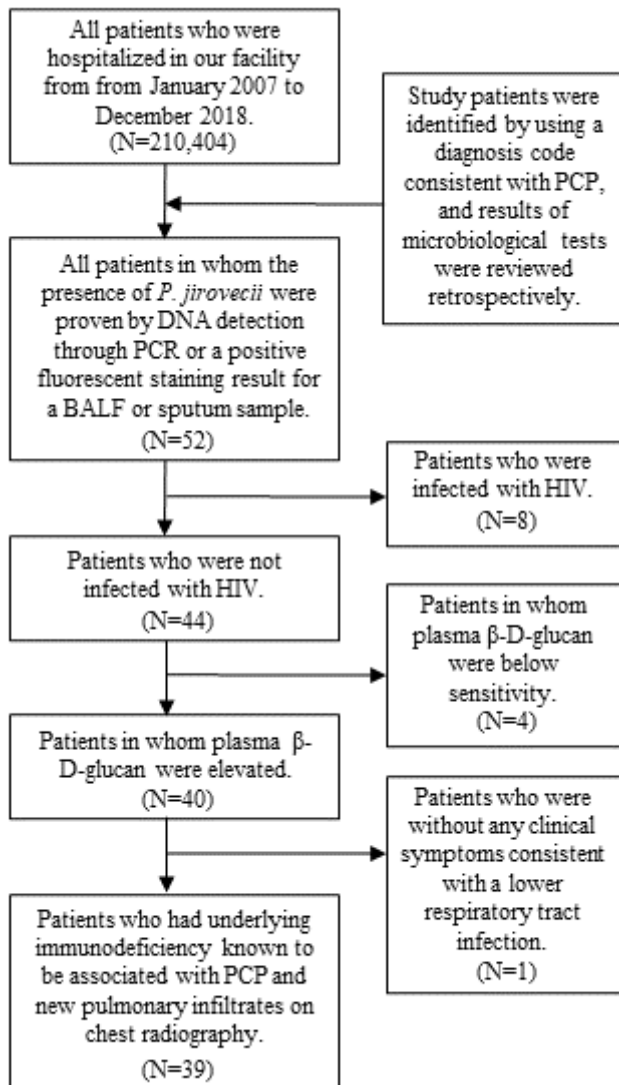
Figures

Figure 1

Inclusion chart for our analysis of 39 patients who were diagnosed with non-HIV PCP. In all, 52 patients had the presence of P. jirovecii proven by deoxyribonucleic acid (DNA) detection through polymerase chain reaction (PCR) or a positive fluorescent staining result for a bronchoalveolar lavage fluid (BALF) or sputum sample. Eight patients were excluded because they were infected with human immunodeficiency virus (HIV), four patients were because their plasma (1−3)-β-D-glucan (β-D-glucan) were below sensitivity

and one patient was because he was without any clinical symptoms consistent with a lower respiratory tract infection. A total of 39 patients were included and analysed.
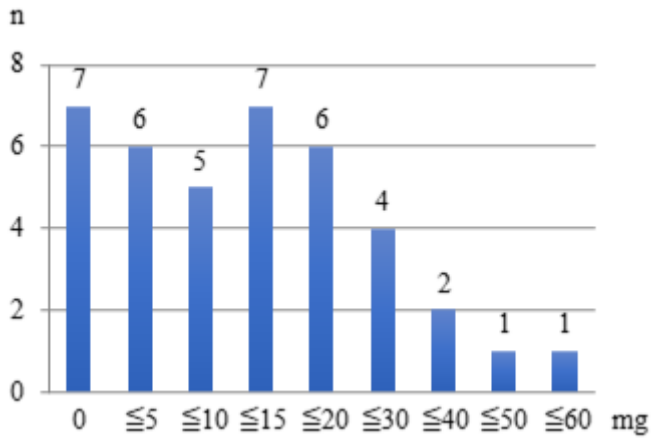

Figure 2

The daily dose of corticosteroid converted to the PSL equivalent dose when PCP developed. Thirty-two patients were treated with corticosteroids. The daily dose of corticosteroid converted to the PSL equivalent dose ranged from 2 to 60 mg. Further, 24, 11, and six patients were administered 20 mg or less, 10 mg or less, and 5 mg or less.
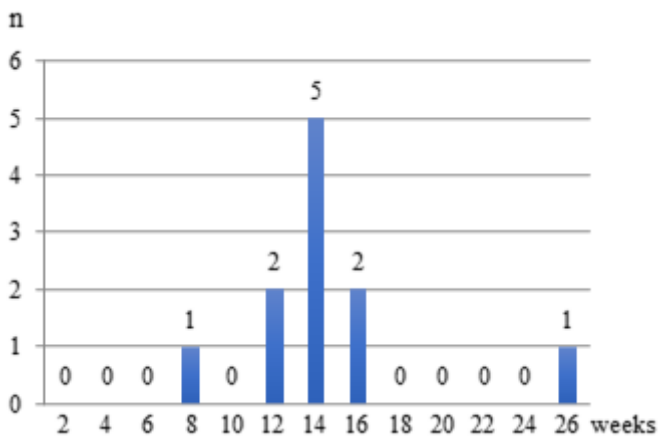

Figure 3

The period from discontinuation of TMP-SMX to development of PCP. The period from discontinuation of TMP-SMX to development of PCP ranged from 44 to 175 days, and in nine patients, PCP developed 14 ± 2 weeks after TMP-SMX discontinuation.

Supplementary Files

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- Table1.xlsx

- Table2.xlsx
- Table3.xlsx