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ORIGINAL ARTICLE

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Prediction of and prophylaxis against *Pneumocystis* pneumonia in patients with connective tissue diseases undergoing medium- or high-dose corticosteroid therapy

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Abstract We performed a retrospective analysis to establish a statistical model for the prediction of *Pneumocystis* pneumonia (PCP) in patients with connective tissue diseases (CTD) undergoing medium- or high-dose corticosteroid therapy, to identify independent risk factors for PCP and to evaluate the efficacy of the prophylactic use of trimethoprim–sulfamethoxazole (TMP/SMX) against PCP. One hundred and twenty-four patients who were receiving the equivalent of or more than 30 mg/day of prednisolone (PSL) were classified into two groups according to the presence (prophylaxis group, $n = 46$) or absence (nonprophylaxis group, $n = 78$) of prophylactic TMP/SMX. We developed a statistical model that was suitable for predicting the development of PCP using a logistic regression analysis. The initial steroid dosage, decreased peripheral blood lymphocyte counts at 2 weeks ($<500/\mu l$), and usage of immunosuppressant during 2 weeks after the institution of PSL (≥ 30 mg/day) were found to independently contribute to the development of PCP. Finally, in the patient group with a defined risk for PCP, a significant prophylactic effect of TMP/SMX was demonstrated. We recommend the prophylactic use of TMP/SMX for patients with CTD undergoing medium- or high-dose corticosteroid therapy who are determined to have a high risk of developing PCP.

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Key words Connective tissue disease (CTD) · Logistic regression analysis · *Pneumocystis* pneumonia (PCP) · Trimethoprim–sulfamethoxazole

Introduction

Pneumocystis pneumonia (PCP) is a serious and potentially fatal infection often encountered in immunosuppressed patients. It is one of the most common opportunistic infections associated with human immunodeficiency virus (HIV) infection,[1–4] and is also observed in other severely immunocompromised patients with cancer, hematological malignancies, or organ transplantation.[5–8] Patients with connective tissue diseases (CTD) are also at risk for PCP. *Pneumocystis* pneumonia affects 2.6%–4.3 % of all patients undergoing treatment for CTD.[9,10] Several studies have analyzed the risk factors for PCP among patients with CTD and have found a relationship between the development of PCP and the administration of high-dose corticosteroids or immunosuppressants.[9,11–13] It has also been demonstrated that some clinical signs and laboratory variables are risk factors for PCP in patients with CTD.[14,15] Godeau et al.[15] used multivariate analysis to report a statistically significant association between developments of PCP and decreased peripheral blood lymphocyte (PBL) counts before as well as after treatment in patients with Wegener's granulomatosis (WG). Kadoya et al.[14] demonstrated that lymphopenia and interstitial pneumonitis (IP) could be risk factors for PCP using univariate analysis in patients with systemic lupus erythematosus (SLE), polymyositis/dermatomyositis (PM/DM) and polyarteritis nodosa (PN) who had been treated with high-dose corticosteroids. However, there has been no report that described a statistical model to predict the probability of developing PCP. Such a statistical model may not only enable us to determine independent risk factors for PCP but also help us to identify the patients at high risk for developing PCP.

A recent study of prophylaxis against PCP in patients infected with HIV has revealed that low-dose trime-

Table 1. Clinical profile of the enrolled patients

Connective tissue disease	No. of cases	
	PCP(−) (n = 115)	PCP(+) (n = 9)
Systemic lupus erythematosus	49	4
Polymyositis/dermatomyositis	14	2
Vasculitis syndrome	12	0
Rheumatoid arthritis	11	1
Adult-onset Still's disease	8	1
Mixed connective tissue disease	7	0
Systemic sclerosis	4	0
Overlap syndrome	1	1
Sjögren's syndrome	2	0
Behçet's disease	1	0
Others	6	0

Others included sarcoidosis, reflex sympathetic dystrophy, Weber–Christian disease, Cogan's syndrome, Evans' syndrome, and necrotizing lymphadenitis
PCP, *Pneumocystis* pneumonia

thoprim–sulfamethoxazole (TMP/SMX) effectively prevented the onset of PCP.[16] The widespread application of TMP/SMX prophylaxis in practice drastically reduced the mortality rate of PCP in patients infected with HIV from 30%–50% to 1%.[17] Okada et al.[10] reported that PCP was not observed in patients with CTD who were treated with more than 40 mg/day of prednisolone (PSL) when TMP/SMX was administered to those with pre-existing IP or lymphopenia. On the other hand, 4.3% of the patients without these clinical features and who did not receive prophylaxis developed PCP. It is difficult to determine the efficacy of prophylaxis with TMP/SMX against PCP in their study, however, because the probability of developing PCP in the patients who did and did not receive the prophylaxis was not evaluated using an appropriate statistical model.

In the present study, we retrospectively identified the clinical features and laboratory variables that were characteristic of CTD patients who developed PCP using univariate analysis. A logistic regression analysis was performed to establish a statistical model for predicting the probability of developing PCP and to determine which of these characteristics represent genuine independent risk factors. The patients at high risk for developing PCP were identified using the statistical model. Finally, we evaluated the efficacy of prophylaxis with TMP/SMX against PCP in these patients.

Patients and methods

Patients

One hundred and twenty-four patients with various CTD who fulfilled the following criteria were enrolled in this study: (1) patients were admitted to the Department of Rheumatology, Tokyo Medical and Dental University Hospital between July 1998 and April 2002; (2) treatment with more than 30 mg/day of PSL was started after admission; and (3) patients were followed up at least 6 months after the institution of PSL. The protocol was reviewed and approved by the local institutional review boards, and patients gave written informed consent. The CTD diagnoses of the patients are summarized in Table 1. To restrict the analysis to the efficacy of prophylaxis with TMP/SMX against PCP, three patients who fulfilled the above criteria receiving prophylactic treatment with pentamidine isothianate, but not with TMP/SMX, were excluded from this study.

Diagnostic criteria of PCP

Pneumocystis pneumonia was diagnosed according to the criteria of a previous report that described prophylaxis against PCP in patients infected with HIV.[18] All of the patients diagnosed with PCP in the present study had the following four features strongly suggestive of PCP: (1) clinical manifestation including pyrexia, dry cough, and dyspnea, (2) hypoxemia ($PaO_2 < 80$ torr) or increase of alveolar oxygen gradient (A-a$DO_2 > 15$ mmHg),[19] (3) diffuse alveolar infiltrates or interstitial infiltrates on chest X-ray as well as on computed tomography of the thorax,[20,21] and (4) increase of serum β-D-glucan level.[22] We diagnosed PCP in nine out of the 124 patients.

Prophylaxis with TMP/SMX against PCP

Prophylaxis with TMP/SMX was instituted when a patient was considered to be at a relatively high risk for PCP by his or her attending physician. One tablet of TMP/SMX contains 80 mg of trimethoprim and 400 mg of sulfamethoxazole (Baktar, Shionogi Pharmaceuticals, Japan). We administered three tablets of TMP/SMX three times a week or one tablet every day.[16,18,23]

Classification of the patients

We classified patients into two groups according to the presence or absence of prophylaxis with TMP/SMX against PCP. Forty-nine patients were administered TMP/SMX, but three of them discontinued it within 7 days (administra-

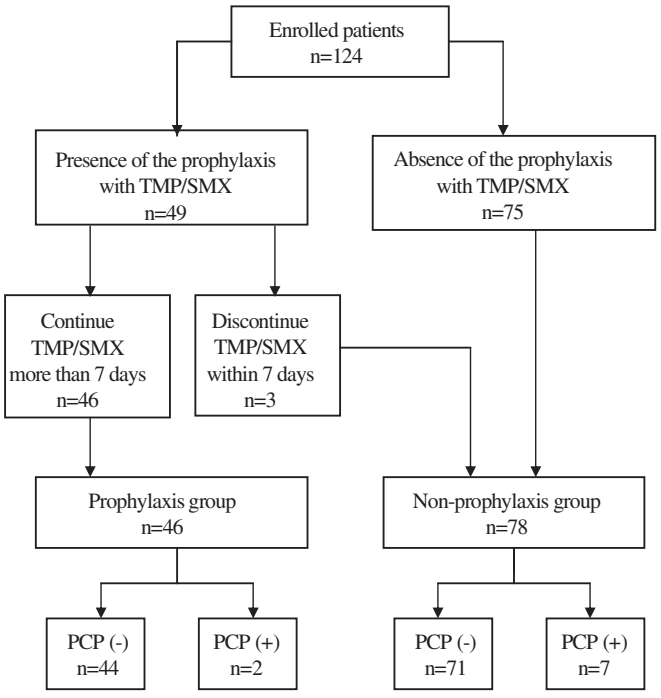

Fig. 1. Classification of the enrolled patients. Forty-six patients who could continue trimethoprim–sulfamethoxazole (TMP/SMX) for more than 7 days were classified as the prophylaxis group and 78 patients who were not administered TMP/SMX or discontinued TMP/SMX within 7 days were classified as the nonprophylaxis group. *PCP*, *Pneumocystis* pneumonia

tion period, minimum–maximum = 3–7 days, median = 5 days) because of adverse drug reactions such as nausea, erythema, renal dysfunction, and cytopenia. The remaining patients (n = 46) continued TMP/SMX for more than 7 days (minimum–maximum = 13–1264 days; median = 248 days). Those who were not administered TMP/SMX (n = 75) or discontinued TMP/SMX within 7 days (n = 3) were classified as the nonprophylaxis group. Those who could continue TMP/SMX more than 7 days (n = 46) were classified as the prophylaxis group. Two and seven patients developed PCP from the prophylaxis and the nonprophylaxis group, respectively (Fig. 1).

Collection of clinical and laboratory data

Clinical and laboratory data were collected from the medical records of the enrolled patients. All patients were treated with oral PSL. Total steroid dosage during 2 weeks after the institution of PSL (≥30 mg/day) was calculated for each patient. When patients additionally received methylprednisolone (mPSL) pulse therapy, the amounts of mPSL administered were converted to the corresponding amounts of PSL and added to the total steroid dosage of the patients. One milligram of mPSL was calculated as being equivalent to 1.25 mg of PSL.[24] Usage of immunosuppressive agents during 2 weeks after the institution of PSL, peripheral blood lymphocytes (PBL) counts before as well as 2 and 4 weeks after the institution of PSL, and serum albumin levels before the institution of PSL were collected from the medical records.

Statistical analyses

To identify clinical and laboratory characteristics of the patients who developed PCP, we compared the seven patients from the nonprophylaxis group who developed PCP and the 71 remaining patients in that group. The 46 patients in the prophylaxis group, two of whom developed PCP, were excluded from this comparison because of the possible effects of TMP/SMX on the prevention of PCP. We used Fisher's exact test for categorical variables and the Mann–Whitney U-test for continuous variables.

A logistic regression analysis was performed with the data from 78 patients in the nonprophylaxis group. In a logistic regression analysis, the risk score (S) for a patient is represented as $S = \beta_0 + \beta_1 X_1 + \cdots \beta_p X_p$, where β_0 is the constant, β_i is the regression coefficient of each predictive variable X_i, and number of predictive variables in a model is p. We selected the best statistical model using a backward elimination method and compared statistical models with different numbers of predictive variables using Akaike's information criteria (AIC).[25] In general, the lower the AIC, the better the fit of the statistical model, a better fit meaning the statistical model predicts the development of PCP more accurately. The risk score (S) was used to calculate the probability of developing PCP, $P(x)$. $P(x)$ is given as $1/(1 + e^{-s})$. Regression coefficients for each predictive variable were used to calculate the odds ratio (OR) and 95% confidence interval (CI) of OR of the corresponding variables. For continuous predictive variables, we also calculated incremental OR.

After selecting the best statistical model, we calculated the $P(x)$ of each patient and evaluated the efficacy of TMP/SMX using Fisher's exact test in patients at a relatively high risk for PCP. Throughout the statistical analysis, we considered P values less than 0.05 (two-tailed) to be statistically significant. All analyses were performed using Stat-View software 5.0 (SAS Institute, Cary, NC, USA).

Results

Clinical and laboratory data of the patients with PCP

We analyzed the clinical and laboratory records of the patients in the nonprophylaxis group (Table 2). We compared age, sex, smoking, prevalence of IP, and diagnosis of CTD, but found no significant difference between patients who did and did not develop PCP (data not shown). When the treatments for CTD were compared, there were significant differences between the two groups in initial steroid dosage (P = 0.005), total steroid dosage (P = 0.006), and usage of immunosuppressive agents (P = 0.014) during 2 weeks after the institution of PSL (Table 2). There was, however, no significant difference between the two groups in the frequency of the usage of each immunosuppressive agent in-

Table 2. Clinical and laboratory data of the patients in the nonprophylaxis group

Clinical and laboratory data	PCP(+) (n = 7)	PCP(−) (n = 71)	P value
Initial steroid dosage (mg/day)	55.7 ± 16.2	38.9 ± 11.8	0.005[a]
Total steroid dosage (mg) (0–2 weeks)	2410 ± 1693	831 ± 903	0.006[a]
Usage of immunosuppressive agents (0–2 weeks)	3/7	4/71	0.014[b]
PBL counts at 2 weeks (/μl)	584 ± 434	1444 ± 933	0.011[a]
PBL counts at 4 weeks (/μl)	440 ± 300	1252 ± 1023	0.004[a]
PBL counts at 2 weeks (<500/μl)	4/7	9/71	0.013[b]
PBL counts at 4 weeks (<500/μl)	4/7	13/71	0.037[b]
Serum albumin before treatment (g/dl)	2.3 ± 0.4	3.1 ± 0.6	0.0017[a]
Serum albumin before treatment (<2.5 g/dl)	4/7	11/71	0.023[b]

Steroid dosages were expressed as corresponding amounts of PSL. Data are expressed as mean ± SD of each group for initial steroid dosage, total steroid dosage, PBL counts at 2 weeks (/μl), PBL counts at 4 weeks (/μl) and serum albumin before treatment (g/dl). Data are expressed as "number of patients receiving the treatment or number of patients having the laboratory data in the group/total number of patients in the group" for usage of immunosuppressive agents (0–2 weeks), PBL counts at 2 weeks (<500/μl), PBL counts at 4 weeks (<500/μl), and serum albumin before treatment (<2.5 g/dl)

PCP, *Pneumocystis* pneumonia; PSL, prednisolone; PBL, peripheral blood lymphocyte

[a] P values calculated using the Mann–Whitney U-test

[b] P values calculated using Fisher's exact test

cluding cyclophosphamide, methotrexate, azathiopurine, and cyclophosphamide (data not shown). When we analyzed the laboratory data, we found that PBL counts 2 weeks after the institution of PSL ($P = 0.011$) and the levels of serum albumin before the institution of PSL ($P = 0.0017$) in the patients who developed PCP were significantly lower than those of the other patients (Table 2). The difference was also significant when these data were analyzed as categorical variables using Fisher's exact test (Table 2). Peripheral blood lymphocyte counts 4 weeks after the institution of PSL, but not before the treatment, in the patients who developed PCP were also significantly lower than those of the other patients (Table 2).

A statistical model for the prediction of the risk for PCP during medium- or high-dose corticosteroid therapy

To predict risk for contracting PCP during medium- or high-dose corticosteroid therapy, we employed a logistic regression analysis. Among several clinical and laboratory data which showed significant difference between the patients with and without PCP, we finally used the following five therapeutic and laboratory data sets as predictive variables of a logistic regression analysis: initial steroid dosage, total steroid dosage during 2 weeks after the institution of PSL, usage of immunosuppressive agents during 2 weeks after the institution of PSL, PBL counts 2 weeks (<500 or ≥500/μl) after the institution of PSL, and level of serum albumin (<2.5 or ≥2.5/μl) before the institution of PSL.

We performed a logistic regression analysis using data from the 78 patients in the nonprophylaxis group and selected the best model by backward elimination method and AIC. In our best model, the risk score (S) of a patient is represented as $S = -8.88 + 0.107 \times A + 2.518 \times B + 4.045 \times C$, where A is initial steroid dosage (mg), B is 1 or 0 if PBL counts 2 weeks after the institution of PSL of the patient was or was not less than 500/μl, and C is 1 or 0 if the patient did or did not use immunosuppressive agents during 2 weeks after the institution of PSL. We calculated the OR and 95%CI of each predictive variable using their regression coefficients in our best model and found that above three predictive variables were statistically significant independent risk factors. The incremental OR for initial steroid dosage by 10 mg was 2.92 (95% CI 1.31–6.51, $P = 0.0083$), OR for PBL counts at 2 weeks <500/μl was 12.4 (95% CI 1.07–144, $P = 0.044$), and OR for usage of immunosuppressive agents was 57.1 (95% CI 1.97–1660, $P = 0.0186$).

We used our best model to calculate the risk score (S) and $P(x)$ values for the 78 patients in the nonprophylaxis group. Sensitivity and specificity of our best model for predicting the development of PCP with various cutoff value of $P(x)$ were calculated using contingency table and were plotted against each $P(x)$ value (Fig. 2). We determined an optimal cut-off value of $P(x)$ as 0.10, shown in Fig. 2. Sensi-

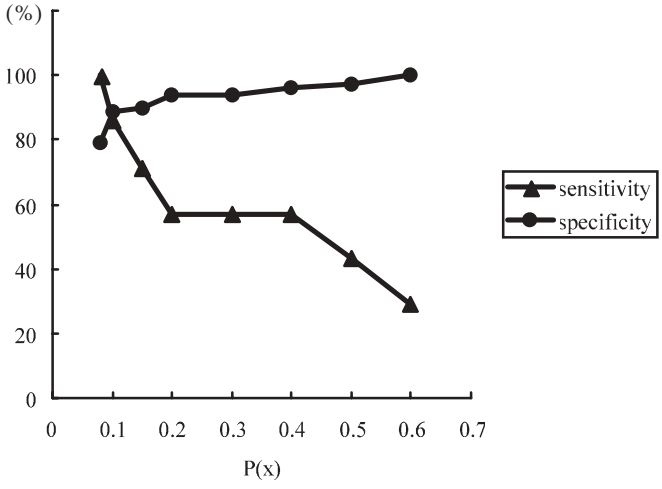

Fig. 2. Sensitivity and specificity of our best model with various cutoff values of $P(x)$. Sensitivity (*triangles*) and specificity (*circles*) of our best model with various cutoff values of $P(x)$ were calculated using contingency tables and plotted against each cutoff value. We determined an optimal cutoff value of $P(x)$ as 0.10 (see text for details)

Table 3. Results of classification using our best model

	PCP(+)	PCP(−)	Total
$P(x) \geq 0.1$	6	8	14
$P(x) < 0.1$	1	63	64
Total	7	71	78

The risk score (S) was calculated for each patient in the nonprophylaxis group ($n = 78$) using our best model and was converted to the probability of developing PCP, $P(x)$, as described in Patients and methods. The patients were divided into $P(x) \geq 0.1$ or $P(x) < 0.1$, and were assigned to the contingency table

Table 4. Efficacy of prophylaxis with TMP/SMX in patients with high risk of PCP

	PCP(+)	PCP(−)	Total
TMP/SMX(+)	2	19	21
TMP/SMX(−)	6	8	14
Total	8	27	35

The predicted probability [$P(x)$] of developing PCP was calculated for all 124 patients using our best model. Patients whose $P(x)$ values were equal to or greater than 0.1 ($n = 35$) were analyzed for the efficacy of prophylaxis with trimethoprim–sulfamethoxazole (TMP/SMX) using Fisher's exact test
$P = 0.039$ by Fisher's exact test

tivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy are 86%, 89%, 43%, 98%, and 89%, respectively (Table 3).

Efficacy of prophylaxis with TMP/SMX in patients with a relatively high risk of developing PCP.

We next evaluated efficacy of the prophylaxis with TMP/SMX in 35 patients whose $P(x)$ values in our best model were equal to or greater than 0.1. Among these 35 patients, TMP/SMX showed significant prophylactic effects against PCP ($P = 0.039$) (Table 4). These data strongly indicate that the administration of TMP/SMX significantly prevented the development of PCP in CTD patients undergoing medium- or high-dose corticosteroid therapy.

Adverse drug reactions of the prophylaxis with TMP/SMX

Three of the 49 patients initially receiving TMP/SMX (6.1%) discontinued the prophylaxis because of the following adverse drug reactions: renal dysfunction in one patient; erythema in one; leukopenia in one; and nausea in one. All of these adverse drug reactions disappeared after the withdrawal of TMP/SMX.

Discussion

In the present study, we demonstrated that: (1) patients with CTD undergoing medium- or high-dose corticosteroid therapy who developed PCP had several common clinical and laboratory characteristics; (2) initial steroid dosage, PBL counts 2 weeks after the institution of PSL $< 500/\mu l$ and usage of immunosuppressants during 2 weeks after the institution of PSL were the independent risk factors for the development of PCP; (3) a logistic regression analysis was useful for establishing a statistical model to predict the development of PCP; and (4) efficacy of prophylaxis with TMP/SMX was suggested for the prevention of PCP in patients at a relatively high risk for PCP.

Several anecdotal case reports have described patients who developed PCP under intensive immunosuppressive therapy for CTD.[9,12] Some investigators performed case control studies to compare CTD patients who did and who did not develop PCP using univariate analysis.[10,14] Clinical and laboratory characteristics showing significant differences between patients who did and did not develop PCP using univariate analysis may not identify independent risk factors. There have been two reports that used a logistic regression analysis and described independent risk factors for PCP.[15,26] However, one study did not include information about treatment or laboratory variables[26] and the other found PBL counts before as well as 3 months after the treatment were independently associated with PCP.[15] To our knowledge, this is the first report that has demonstrated initial steroid dosage and usage of immunosuppressants during 2 weeks after the institution of PSL as independent risk factors for the development of PCP in patients with CTD using a logistic regression analysis. It should also be mentioned that all three predictive variables in our statistical model are available within 2 weeks after the institution of PSL, which enables us to predict development of PCP at an early stage of medium- or high-dose corticosteroid therapy. In the present study, we could not analyze risk factors for PCP in each CTD since we had only nine patients with PCP. Such analysis may enable us to predict PCP more accurately in individual patients.

Since PCP is a potentially fatal infectious disease, it is ethically impossible to withhold the administration of TMP/SMX in patients at high risk for PCP in order to analyze the efficacy of the prophylaxis. We therefore applied the statistical model to our patients and calculated their probability of developing PCP. Using our statistical model, the efficacy of prophylaxis with TMP/SMX in patients at a high risk for developing PCP was strongly suggested (Table 4). There has been no report that has successfully applied a statistical model to predict the risk for developing PCP and demonstrated the efficacy of prophylaxis with TMP/SMX in CTD patients with a statistically defined risk for developing PCP.

Patients with CTD are also exposed to a significant risk for other opportunistic infections such as cytomegalovirus infection and tuberculosis because of intense immunosuppressive treatments. Since these infectious diseases are less common than PCP among the patients with CTD in our hospital, we could not analyze predictive variables for these diseases. In patients with simultaneous kidney–pancreas transplantation and hematopoietic stem cell transplants, hypoalbuminemia (<3.5 g/dl) and lymphocytopenia ($<300/$

μl) have been reported as risk factors for cytomegalovirus infection.[27,28]

In conclusion, it is strongly recommended that patients with CTD receiving medium- or high-dose corticosteroid therapy and an immunosuppressant with decreased number of PBL be closely monitored for the development of PCP. Prophylaxis with TMP/SMX should be considered in patients at high risk for PCP for the successful treatment of CTD.

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Erratum

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An error appeared in the article cited above. On page 6, the last line of Figure 1 incorrectly shows "(INH, 0.3 mg/ day)". It should read "(INH, 0.3 g/day)".