Sulfasalazine as a prophylactic for pneumocystis pneumonia in patients with rheumatoid arthritis: a cohort study

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Running title: Sulfasalazine as a prophylaxis for pneumocystis pneumonia

Author contributions: NA conceived the study. MY, NA, and M. Kono were responsible for data collection, acquisition, and analysis. MY drafted the manuscript with NA, and M. Kono. KO contributed to the design and statistical methods. All authors (MY, NA, M. Kono, YF, M. Kato, OA, and TA) provided a critical revision of the manuscript and approved the final version to be submitted for publication. All authors take full responsibility for the integrity and accuracy of the work in all aspects.

Funding No specific funding was received to carry out the work described in this manuscript.

Declaration of conflict of interest

M. Kono reports grants and/or speaking fees from AbbVie, Actelion, Asahi-Kasei, Astellas, AstraZeneca, AYUMI, Bristol-Myers Squibb, Chugai, Daiichi Sankyo, Eisai, Eli Lilly, Gilead Sciences, GlaxoSmithKline, Janssen, Kowa, KYOCERA, LOTTE, Nippon Boehringer Ingelheim, NIPPON SHINYAKU, Mitsubishi Tanabe, MOCHIDA, Otsuka, Pfizer, Taiju Life Social Welfare Foundation, Taisho, Takeda, Terumo, UCB Japan and YAMAZAKI BAKING, outside the submitted work. K. Oba participated in a data safety monitoring board or advisory board of Chugai and Daiichi Sankyo and received speaker's bureau from Eisai, Ono, and Janssen. M. Kato has received research grants and speaker's bureau from AbbVie, Janssen, Nippon Shinyaku, Novartis, Astellas, Eli Lilly, outside the submitted work. T. Atsumi has received grants, consulting fee or speakers' bureau from Astellas, Mitsubishi Tanabe, Chugai, Daiichi Sankyo, Pfizer, TEIJIN, Novartis, Sanofi, GlaxoSmithKline, AbbVie, AstraZeneca, Nippon Boehringer Ingelheim, Janssen, Gilead Sciences, Eli Lilly, ONO, Takeda, Alexion, Kyowa Kirin, Amgen, UCB Japan, and Esai, outside the submitted work. The other authors have no competing interests to declare.

Keywords: Sulfasalazine, Pneumonia, Pneumocystis, Arthritis, Rheumatoid,

Abstract

Aim: We investigated the potential of Sulfasalazine (SSZ), one of the conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), as primary prophylaxis for pneumocystis pneumonia (PCP) in patients with rheumatoid arthritis (RA).

Methods: In this longitudinal cohort study, we enrolled patients with RA who started receiving new RA treatment. A treatment episode was defined as a period of 1 year from the start or increase of DMARDs dose, or started prednisolone >10 mg/day, and the incidence of PCP in this period was assessed. All treatment episodes were classified into two groups based on the presence of SSZ at baseline. The PCP incidence rate in the two groups was evaluated using a negative binomial regression model.

Results: A total of 848 treatment episodes were recorded in 594 RA patients: 181 and 667 in the SSZ and control groups, respectively. During the 850.6 person-years of observation, 21 patients developed PCP, and 3 died of PCP. Multivariable adjusted analysis using Firth's method showed that the 1-year incidence of PCP was significantly reduced with SSZ treatment (P = 0.003, rate ratio = 0.05; 95% CI 0.00-0.34). Furthermore, the log-rank test in the propensity score-matched population confirmed this result. Regarding safety, 45 adverse drug reactions related to SSZ occurred (4.34/100 person-years; 95% CI 3.26-

5.78). Only one serious adverse reaction (drug-induced hypersensitivity syndrome) was observed, which resolved after discontinuation of SSZ.

Conclusion: We demonstrated the preventive efficacy of SSZ on PCP. The pleiotropic effect of this traditional DMARD may impact RA treatment, providing another option for PCP prophylaxis.

Introduction

Pneumocystis pneumonia (PCP), caused by *Pneumocystis jirovecii*, is one of the most common opportunistic infections [1-3], and an indicator of acquired immunodeficiency syndrome (AIDS). Previously, PCP was the most common cause of death in patients with AIDS, but effective antiretroviral therapy and prophylactic strategies with sulfamethoxazole/trimethoprim (SMX/TMP), also termed co-trimoxazole, have resulted in a marked decline in incidence [4]. However, PCP is a serious and potentially life-threatening comorbidity in non-human immunodeficiency virus (HIV)-infected immunocompromised patients, including those with rheumatic diseases [5-7]. The risk factors for developing PCP in non-HIV patients include the use of immunosuppressive drugs, concomitant malignancies, chemotherapy, hemodialysis, and solid organ transplantation [8, 9]. Therefore, patients with these factors are more likely to benefit from PCP prophylaxis. SMX/TMP is also effective to prevent PCP prophylaxis in patients with rheumatic diseases [10-13]. A previous study in patients with rheumatoid arthritis (RA) have identified the following risk factors for PCP and recommends the prophylaxis with SMX/TMP in those having two or more risk factors: age 65 years or older, use of prednisolone at 6 mg/day or higher, or other comorbidities of pulmonary diseases [14]. In addition, several reports also suggest that glucocorticoid use itself,

regardless of dose, may increase the risk of PCP, implying that even low-dose corticosteroid therapy should not be overlooked when the risk is assessed [15-17]. SMX/TMP use generally may be limited due to intolerable adverse drug reactions, such as skin rash, liver damage, electrolyte disorders, and bone marrow suppression, especially in older adults, who often have reduced organ function and multiple comorbid conditions [18]. Drug interactions have also been observed between SMX/TMP and a number of medications [19]. Moreover, there is no consensus on the optimal regimen for primary prophylaxis of PCP in patients with RA, as its incidence and the risk-benefit of prevention remain unclear.

Sulfasalazine (SSZ), also called salazosulfapyridine, is a one of the most frequently used conventional synthetic disease-modifying antirheumatic drugs (csDMARDs). SSZ was developed in 1942 as a treatment for RA and was synthesized via the azo bond of sulfapyridine (SP), an antibacterial agent, and 5-aminosalicylic acid, an anti-inflammatory agent, as it used to be thought that RA was caused by infection in the past [20, 21]. Sulfonamide-containing drugs, including sulfamethoxazole (SMX), are believed to exert antipneumocystis activity through competitive inhibition of the *P. jirovecii* enzyme dihydropteroate synthetase [22, 23]. SP is also a sulfa drug that shares a sulfonamide structure with sulfamethoxazole. Several studies have revealed that SSZ

enhances *Pneumocystis* clearance by accelerating alveolar macrophage phagocytosis [24, 25] and unlike other sulfamides, SSZ may have a unique action against PCP. However, to date, there is little evidence that SSZ can be used safely as a primary prophylaxis for PCP. Thus, this study investigated the efficacy and safety of SSZ as primary PCP prophylaxis in adult patients with RA.

Materials and methods

Participants and study design

This single-centre, retrospective cohort study was conducted at Hokkaido University Hospital in accordance with the ethical principles of the Declaration of Helsinki and the Good Clinical Practice guidelines approved at the Hokkaido University Hospital Certified Review Board (approval number: 019-0146). The electronic medical database of Hokkaido University Hospital was reviewed to identify RA patients who had newly started treatment with dose escalation of csDMARDs, targeted synthetic DMARDs (tsDMARDs), or biologic DMARDs (bDMARDs), or started treatment with prednisolone (PSL) >10 mg/day between January 2006 and July 2021. All the patients met the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria [26]. In this study, the csDMARDs included methotrexate

(MTX), tacrolimus (TAC), and iguratimod (IGT). The bDMARDs were comprised of five antitumor necrosis factor (TNF) agents (infliximab, adalimumab, etanercept, golimumab, and certolizumab), two anti-interleukin-6 (IL-6) agents (tocilizumab and sarilumab), abatacept, and rituximab. The tsDMARDs were comprised of five Janus kinase inhibitors (JAKi) (baricitinib, filgotinib, peficitinib, tofacitinib, upadacitinib). Patients with a history of PCP, HIV infection, cancer, or solid organ transplantation, or those under 18 years of age were excluded. Patients who received antimicrobial agents such as SMX/TMP, dapsone, atovaquone, or pentamidine for the primary prevention of PCP during the observation period were also excluded.

The baseline was set as the date of the initiation of a treatment episode defined as 1 year from new initiation or increase of DMARDs dose, or started > 10 mg/day PSL as described above. The observation period for each treatment episode was defined as based on previous reports which stated that PCP often occurs within the first year of treatment [27]. In case the treatment was intensified or changed more than one year after the baseline date, it was counted as a separate treatment episode (Figure S1). Since the maximum dose approved in Japan is 1 g/day, the use of SSZ at a dose of 500 mg/day or 1 g/day, was recorded. All treatment episodes were then recorded and classified into two groups, the SSZ and control groups, according to whether or not concomitant SSZ had

been prescribed to each patient at the start of each treatment episode. Treatment episodes in which there was a change of treatment dose or when there was discontinuation of the SSZ during the one-year observation period were excluded.

Endpoints

The primary endpoint was the incidence of PCP in each group according to the treatment episodes during the observation period. The secondary endpoints were PCP-associated mortality and incidence of SSZ-related adverse events. All suspected adverse events were investigated, and events with a potential causal relationship were identified based on the timing and known patterns of side effects.

Detection of PCP

The electronic records of eligible patients with RA were screened to identify all PCP cases during the observation period. In this study, PCP events were defined on the basis of the criteria reported previously [28]. A diagnosis of PCP was made when *P. jirovecii* cysts were detected in patients' respiratory specimens by immunofluorescence staining and/or a real-time quantitative polymerase chain reaction (PCR) test for *P. jirovecii* DNA, as well as the elevation of the serum β-D-glucan level, in addition to

clinical features (fever, dry cough, or acute dyspnea), hypoxemia, and characteristic chest computed tomography (CT) findings compatible with PCP.

Evaluation of SSZ safety

To examine the safety of SSZ, all SSZ-related adverse drug reactions in patients who met the inclusion criteria during the overall treatment period were assessed. Adverse drug reactions were retrospectively identified based on medical record information and changes in laboratory data. Mild adverse drug reactions were defined as awareness symptoms and unpleasant reactions which did not limit daily life; moderate reactions were defined as those that interfered with daily life, but were usually ameliorated by simple outpatient treatment; and serious adverse reactions were defined as reactions that significantly limited daily life and resulted in hospital admission, in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events Version 5 [29].

Variables

Bone erosion was confirmed by radiographs at baseline. We defined positivity of each rheumatoid factor (RF) and anti-citrullinated peptide antibody (ACPA) based on

their normal range (RF <16 IU/mL, ACPA <4.5 U/mL). Patients with diabetes mellitus (DM) were defined as those who used any antidiabetic medication or had a plasma hemoglobin A1c > 6.5% [30]. Rheumatoid arthritis-associated lung disease (RA-LD) was defined as interstitial lung disease, bronchiectasis, or pleural disease diagnosed using chest radiography or CT scan [31]. A positive smoking history was defined as current or past smoking for a total of 10 pack-years or longer [32]. The Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI) were collected at baseline to assess disease activity. SDAI is based on the simple summation of the 28-tender joint count (TJC28) and 28-swollen joint count (SJC28), patient global assessment of disease activity (PGA visual analogue scale [VAS] 0–10 cm), physician global assessment of disease activity (EGA VAS 0-10 cm), and CRP (mg/dL). CDAI is based on the simple summation of the counts of TJC28, SJC28, PGA, and EGA [33].

Statistical analysis

Baseline continuous or categorical data were compared using the Wilcoxon's rank sum test or the chi-square test. In the efficacy analysis, we set up two scenarios to add to the rigor of this study: the first scenario, as a primary analysis, including all

treatment episodes of enrolled patients and the second scenario including only the first treatment episode of enrolled patients. For the analysis of the first scenario, rate ratios (RR) were estimated using a negative binomial regression model with a log link to account for multiple events in some individuals [34]. The total number of episodes experienced by each individual was treated as the outcome, and the total follow-up time (in months) was included as an offset term using its natural logarithm, to account for varying lengths of observation across individuals. Because the number of events was very low, the Firth's penalization approach was used to estimate RRs with %flacpoisson SAS macro (https://github.com/georgheinze/flicflac). Age, sex, DM, and concomitant dose of glucocorticoids were adjusted for in the multivariable model. In addition, least squares mean was used for calculating the adjusted rate ratio of each group. For the second scenario restricted to the first episodes, one-to-one propensity score (PS) matching was performed using nearest neighbor matching with a caliper of 0.20 to correct for differences between groups with respect to baseline characteristics, including patient age, sex, positivity for RF and/or ACPA, disease duration, cumulative steroid dose in the 6 months prior to baseline, concomitant use of glucocorticoid, MTX, TAC, IGT, bDMARDs, or tsDMARDs, concomitant dose of steroid, MTX, and presence of RA-LD, DM, and lymphopenia (<1000/μL) as predictors of the need for prevention. The

differences between the two groups before and after matching was assessed by calculating the standardized difference (Std. diff.). A Std. diff. of < 0.10 suggested adequate variable balance after PS matching. After matching, we estimated the Kaplan-Meier curves for each group and used a log-rank test to assess between-group differences in PCP-free survival. P values less than 0.05 were considered statistically significant. We have handled missing data using complete-case analysis. Statistical analyses were performed using R version 4.2.0 and SAS 9.4.

Results

Patient and treatment episodes characteristics

A total of 848 treatment episodes from 594 patients met the criteria for analysis, among them 181 in patients treated with SSZ (SSZ group), with most patients receiving 500 mg twice daily (170/181 patients, 93.9 %). The baseline characteristics of the SSZ and control groups are presented in Table 1. All patients had complete data on treatment, comorbidity, and clinical outcome. Some patients had missing data for a few variables (bone erosion, smoking status, lymphocyte count, RF, ACPA, and disease activity). Patients in the SSZ group were older, had a higher rate of DM and pulmonary disease, were more likely to be treated with glucocorticoids and csDMARDs other than MTX, and

less likely to use bDMARDs or molecular targeted agents. The baseline measures of disease activity in the two groups were comparable. In addition, we assessed the number of patients who received 3 or more immunosuppressants with or without biologics/tsDMARDs to ascertain whether there has been any difference in immunosuppressive status between the two groups. For this analysis, we defined immunosuppressive agents as including MTX, TAC, and > 10 mg/day PSL, based on their recognized immunosuppressive potential. We identified 4 patients (2.2%) in the SSZ group and 12 patients (1.7%) in the control group, indicating no substantial imbalance in the degree of immunosuppression between the groups. A similar trend was observed in the analysis restricted to the first episode before PS matching (Table 2), and these baseline imbalances were reduced in the post-matched population (Table 3).

During 850.6 person-years of observation, 21 patients developed PCP. The incidence rate (95% CI) in the control group was 2.47 (1.62-3.77) /100 person-years. Fourteen (66.7%) patients developed PCP during the first 6 months; interestingly, none in the SSZ group developed PCP. Notably, SSZ was discontinued two months prior to the baseline in two patients who developed PCP in the control group. Of the PCP cases, *P. jirovecii* was detected in induced sputum or BAL specimens and PCR testing was positive in seven patients (Table S1). Four patients required mechanical ventilation, and three

patients died. All PCP cases were treated with SMX/TMP and a high dose of prednisolone. We also assessed the number of patients with 3 or more treatment episodes as a potential indicator of difficulty to treat. A total of 43 such patients were identified: 10 (8.0%) in the SSZ group and 33 (7.0%) in the control group, with no significant difference between the two groups.

Prophylactic effect and safety of SSZ

In the treatment episodes analysis, univariable analysis showed that age, ILD, DM, and baseline concomitant dose of glucocorticoids were associated with the incidence of PCP, whereas multivariable analysis showed that SSZ administration, in addition to the known risk of developing PCP, significantly reduced the 1-year incidence of PCP (Table 4). The adjusted RR of SSZ administration was 0.05 (95% confidence interval (CI), 0.00 to 0.34, P value = 0.0003), with the adjusted incidence rates based on the least squares means estimated at 0.09 per 100 person-years in the SSZ group and 1.83 per 100 person-years in the control group. In the second scenario, these results were confirmed by the log-rank test in the PS-matched population using only the first treatment episode, which showed that the 1-year incidence of PCP was significantly reduced by prophylactic administration (Figure 1). In addition, a sensitivity analysis was conducted to determine

the robustness of the results, considering that the exclusion of off-support cases in the post-PS matched population may not represent the characteristics of all enrolled cases. In the overall population of 594 patients, negative binomial regression model was applied to PCP incidence as an outcome, and multivariable analyses also showed a significant reduction in PCP incidence with SSZ treatment (Table S2).

In the entire population, 233 out of 594 patients received SSZ at some point during the observation period. During the 1036.7 person-years of SSZ administration, 45 adverse drug reactions (of any type) occurred (4.34/100 person-years; 95% CI 3.26-5.78); 44% (20/45) of patients developed an adverse drug reaction within one month from the SSZ initiation. The most common symptom was skin rash (1.54/100 patient-years), followed by gastrointestinal manifestations (1.16/100 patient-years) (Table 5). The severity of the adverse drug reaction was mostly mild to moderate (44/45, 94.4%). The only serious adverse reaction that resulted in prolonged hospitalization was one case of drug-induced hypersensitivity syndrome (0.67/100 person-years, 95% CI 0.32 to 1.41). However, this case was resolved after SSZ was discontinued. In addition, a risk-benefit analysis of the prophylactic administration of SSZ was performed. The number needed to harm was 233 (95% CI 79 to ∞), based on one case of a serious adverse drug reaction, while the number needed to treat to prevent one case of PCP in all patients was 32 (95%

CI 23 to 57).

Discussion

In this retrospective cohort study, SSZ, a traditional csDMARD, was useful for primary prophylaxis of PCP in adult patients with RA. The treatment of RA has progressed dramatically with the establishment of early diagnostic methods and the assessment of disease activity using a treat-to-target strategy, as well as the emergence of b/tsDMARDs, such as TNF inhibitors and IL-6 inhibitors, and molecularly targeted antirheumatic drugs such as JAK inhibitors[35]. Consequently, more attention should be paid to infectious complications, which could be potentially serious and have a critical impact on patient prognosis. Pulmonary infections, including PCP, are the major cause of death in RA patients, and appropriate risk management is essential [36].

Although MTX is the first-line DMARD for the treatment of RA according to the current guidelines, SSZ is used in several situations, such as in patients with renal impairment or liver dysfunction makes the use of MTX difficult [35]. SSZ can also be used for women in the perinatal period [37]. In the RA population in this study, it was observed that prior to PS matching, patients on SSZ treatment were older, had more comorbidities of DM and lung diseases, and more concomitant PSL than patients without

SSZ. This suggests that SSZ tend to be used in patients at a high risk of infection or organ dysfunction due to age or other factors, and highlights the current position of SSZ in the treatment of RA. The imbalance between groups at baseline was reduced by PS matching, although the covariate of use of immunosuppressive drugs such as rituximab or abatacept after PS matching showed a Std. diff. of >0.1. However, in the PS-matched population, none of the patients receiving rituximab or abatacept developed PCP. Since these agents are generally associated with an increased risk of PCP, and their use was more common in the SSZ group, any potential bias due to this imbalance would likely lead to an underestimation of the protective effect of SSZ. Therefore, the impact of this residual imbalance on the outcome is considered minimal.

Our findings are consistent with two previous Japanese studies, which showed that SSZ administration was significantly associated with a reduction in PCP development in RA patients [38, 39]. These studies have potential weaknesses due to their case-control design, with insufficient evaluation of confounders such as patients' characteristics and comorbidities between cases and controls, as well as the inability to assess the incidence of PCP. We conducted a cohort study to assess the incidence of PCP and the efficacy of SSZ administration; accordingly, it was possible to adjust for several confounders through multivariable analysis and PS-matching analysis. We modelled the risk of PCP using two

different analyses, which were added to the rigor of this study.

This study also provides the assessment of adverse drug reactions associated with SSZ administration, and clinically meaningful information that SSZ has the potential for safe and widespread use. Although SMX/TMP is the first-line drug for PCP prophylaxis [1, 5], it is nevertheless associated with a relatively high rate of adverse drug reactions and interactions [18], and its use is often difficult in patients with risk factors for PCP. SMX, which is a sulfonamide antimicrobial agent, has been commonly reported as a cause of drug allergy and is associated with a variety of hypersensitivity reactions. TMP, which inhibits the synthesis of tetrahydrofolate from dihydrofolate and is believed to work synergistically with SMX, is also known to result in side effects, including hyperkalemia, renal injury, and drug interactions [40]. SSZ and SMX/TMP have a sulfa group and are often associated with similar adverse drug interactions, such as skin rashes [41]. This study assessed the incidence of adverse drug interactions in patients with a history of SSZ treatment, demonstrating that the side effects were often mild and could be used safely. SSZ can also be used without contraindications, except in patients with hypersensitivity to sulfa drugs, which may facilitate its use in the elderly and dialysis patients. SSZ is a reasonably effective anti-rheumatic drug that is available for use in combination with other drugs, is inexpensive, and relatively safe; furthermore, the new

knowledge provided in this study about its primary prophylactic effect on PCP might make SSZ more valuable. Specifically, it may facilitate the use of SSZ in patients with preexisting lung involvement that make MTX difficult to use and who are at relatively high risk for PCP, and it may reserve the use of additional PCP prophylaxis in patients who have already received SSZ. In the present study, PCP cases were not observed in patients treated with 500 mg once daily of SSZ. Compared to the 500 mg twice daily group, this subgroup exhibited a trend toward lower disease activity and a lower incidence of lymphopenia (Table S3). However, the small sample size precludes definitive conclusions regarding clinical differences associated with SSZ dosage or its potential dose-dependent association with PCP risk. Further investigations are necessary to elucidate the influence of SSZ dose on the development of PCP.

This study has some limitations that affect the generalizability of the results. First, the baseline characteristics of the SSZ and non-SSZ groups were not aligned, which is an inevitable limitation of retrospective observational studies, opening the possibility of confounding. We rigorously balanced the SSZ and control groups with respect to covariates a priori thought to be associated with the likelihood of receiving SSZ or not and incidence of PCP with PS matching. However, unmeasured characteristics could not be balanced. Second, although the gold standard for the diagnosis of PCP is the detection

of the organism in respiratory specimens [1], this study included some patients who did not undergo this test, which may have led to overdiagnosis. The picture of PCP differs between HIV and non-HIV positive patients, including those with RA, as the latter tend to have less *P. jirovecii* in the lungs at the onset of PCP. PCP in non-HIV patients usually has a rapid onset, so it is assumed that it is often necessary to initiate treatment regardless of whether or not the causative organism has been identified. All patients in our study were treated with prednisolone and SMX/TMP, and responded to the initial treatment, making it unlikely that some cases were misclassified. Finally, in the present study, the number of PCP cases was small, which could have led to a complete separation of PCP cases in the SSZ and non-SSZ groups, resulting in a large standard error.

Conclusion

In conclusion, this study verified the primary prophylactic effect of SSZ against PCP in patients with RA. The pleiotropic effect of this traditional DMARD would broaden the options for the treatment of RA even in the era of biologics and JAK inhibitors.

Availability of data and materials

Data that underlie the results presented here will be shared upon reasonable request, while preserving patient anonymity. Requests should be sent to the corresponding author at m-kono@med.hokudai.ac.jp.

Declarations/Ethical approval

This study and protocol were conducted in accordance with the ethical principles of Declaration of Helsinki and the Good Clinical Practice guidelines approved by Hokkaido University Hospital Ethics Committee (approval number: 019-0146).

Informed consent

Patients were not required to give informed consent to this study because the analysis used anonymous clinical data for retrospective study.

Supplementary materials

Supplementary materials are available at the online version.

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Table 1. Baseline Clinical Characteristics of the Whole Episodes

Characteristics	Control (n=667)	SSZ use (n=181)	P value
Female gender, n (%)	566 (84.9)	141 (77.9)	0.03
Age, year, median (IQR)	59 (48-67)	63 (54-71.5)	<0.0001
Duration, year, median (IQR)	2 (0-8)	3 (0-9)	0.10
Smoking history, n (%)	206 (42.0)	77 (52.0)	0.03
Bone erosion, n (%)	328 (49.4)	86 (48.3)	0.79
RF, n (%)	478 (72.0)	128 (71.1)	0.82
ACPA, n (%)	454 (70.5)	121 (68.4)	0.58
Interstitial lung disease, n (%)	65 (9.7)	30 (16.6)	0.01
Diabetes mellitus, n (%)	53 (7.9)	26 (14.3)	0.008
Concomitant medications			
GC use, n (%)	314 (47.1)	104 (57.5)	0.02
GC dose, mg/day, median (IQR)	0 (0-5)	2.5 (0-5))	0.06
MTX use, n (%)	552 (82.8)	118 (65.2)	<0.0001
MTX dose, mg/week, median (IQR)	8 (6-10))	6 (0-10)	<0.0001
b/tsDMARDs, n (%)	297 (44.5)	65 (35.9)	0.04
TNF-α inhibitors *	142 (21.2)	25 (13.8)	0.02

IL-6 inhibitors †	86 (12.9)	17 (9.4)	0.24
Abatacept	48 (7.1)	20 (11.1)	0.09
JAK inhibitors ‡	28 (4.2)	4 (2.2)	0.21
Rituximab	3 (0.5)	1 (0.6)	0.86
Tacrolimus, n (%)	44 (6.6)	29 (16.9)	<0.0001
Iguratimod, n (%)	22 (3.3)	22 (12.2)	<0.0001
Lymphocytopenia (<1000 /μL), n (%)	105 (16.5)	22 (13.0)	0.27
CDAI, median (IQR)	16 (9-24)	15.7 (11.2-23.1)	0.83
SDAI, median (IQR)	16.7 (9.8-26.2)	17.7 (12.9-24.7)	0.45

* TNF-α inhibitors were comprised of infliximab, adalimumab, etanercept, golimumab, and certolizumab pegol. † IL-6 inhibitors were comprised of tocilizumab and sarilumab. ‡ JAK inhibitors were comprised of baricitinib, filgotinib, peficitinib, tofacitinib, upadacitinib.

IQR: interquartile range, SSZ: sulfasalazine, RF: rheumatoid factor, ACPA: anti-citrullinated peptide antibody, GC: glucocorticoid, MTX: methotrexate, bDMARDs: biological disease-modifying antirheumatic drugs, TNF: tumor necrosis factor, IL-6: interleukin-6, JAK: janus kinase, SDAI: the Simplified Disease Activity Index, CDAI: the Clinical Disease Activity Index.

Table 2. Baseline Clinical Characteristics of the Whole Population with the first episode

Characteristics	Control (n=469)	SSZ use(n=125)	P value	std.diff
Female gender, n (%)	392 (83.6)	94 (75.2)	0.031	0.21
Age, year, median (IQR)	59.0 (47.0-67.0)	64.0 (53.0-71.5)	<0.001	0.43
Duration, year, median (IQR)	1.0 (0.0-7.0)	1.0 (0.0-8.5)	0.246	0.04
Smoking history, n (%)	155 (45.5)	47 (48.0)	0.730	0.05
Bone erosion, n (%)	226 (48.5)	55 (45.1)	0.542	0.07
RF, n (%)	344 (73.8)	84 (67.7)	0.177	0.13
ACPA, n (%)	326 (73.3)	81 (66.4)	0.141	0.15
RA-LD, n (%)	51 (10.9)	21 (16.8)	0.089	0.17
Diabetes mellitus, n (%)	45 (9.6)	17 (13.6)	0.192	0.13
Cumulative GC dose, mg, median (IQR)	0.0 (0.0-450.0)	0.0 (0.0-750.0)	0.052	0.14
Concomitant medications				
GC use, n (%)	227 (48.4)	72 (57.6)	0.070	0.19
GC dose, mg/day, median (IQR)	0.0 (0.0-5.0)	2.5 (0.0-5..0)	0.243	0.02
MTX use, n (%)	395 (84.2)	88 (70.4)	<0.001	0.33
MTX dose, mg/week, median (IQR)	8.0 (6.0-10.0)	6.0 (0.0-10.0)	0.004	0.31
b/tsDMARDs, n (%)	195 (41.6)	35 (28.0)	0.005	0.29

TNF inhibitors *	94 (20.0)	15 (12.0)	0.038	0.22
IL-6 inhibitors †	54 (11.5)	9 (7.2)	0.192	0.15
Abatacept	37 (7.9)	12 (9.6)	0.582	0.06
JAK inhibitors ‡	16 (3.4)	0 (0.0)	0.030	0.27
Rituximab	1 (0.2)	1 (0.8)	0.377	0.08
Tacrolimus, n (%)	25 (5.3)	17 (13.6)	0.003	0.29
Iguratimod, n (%)	7 (1.5)	6 (4.8)	0.004	0.19
Lymphocytopenia (<1000 /μL), n (%)	72 (16.1)	17 (14.4)	0.776	0.05
CDAI, median (IQR)	18.0 (11.9-26.4)	15.8 (10.9-23.2)	0.323	0.18
SDAI, median (IQR)	19.5 (12.2-28.1)	17.7 (13.0-24.1)	0.511	0.13

* TNF-α inhibitors were comprised of infliximab, adalimumab, etanercept, golimumab, and certolizumab pegol. † IL-6 inhibitors were comprised of tocilizumab and sarilumab. ‡ JAK inhibitors were comprised of baricitinib, filgotinib, peficitinib, tofacitinib, upadacitinib.

Std.diff: standardized difference, IQR: interquartile range, SSZ: sulfasalaizine, RF: rheumatoid factor, ACPA: anti-citrullinated peptide antibody, RA-LD: rheumatoid arthritis-associated lung disease, GC: glucocorticoid, MTX: methotrexate, b/tsDMARDs: biological or targeted synthetic disease-modifying antirheumatic drugs, TNF: tumor necrosis factor, IL-6: interleukin-6, JAK: janus kinase, SDAI: the Simplified Disease Activity Index, CDAI: the Clinical Disease Activity Index.

Table 3. Baseline Clinical Characteristics of PS-matched Population with the first episode

Characteristics	Control (n=111)	SSZ use (n=111)	P value	Std.diff
Female gender, n (%)	84 (75.7)	85 (76.5)	0.87	0.02
Age, year, median (IQR)	65 (55.0-73.0)	65 (53.0-72.0)	0.99	0.02
Duration, year, median (IQR)	1.0 (0.0-7.0)	0.0 (0.0-5.0)	0.30	0.02
Smoking history, n (%)	33 (49.3)	39 (48.1)	0.89	0.02
Bone erosion, n (%)	52 (42.3)	49 (45.0)	0.73	0.05
RF, n (%)	73 (65.7)	75 (67.6)	0.78	0.04
ACPA, n (%)	68 (65.4)	70 (64.8)	0.93	0.01
RA-LD, n (%)	18 (16.2)	16 (14.4)	0.71	0.05
Diabetes mellitus, n (%)	15 (13.5)	16 (14.4)	0.85	0.03
Cumulative GC dose, mg, median (IQR)	0.0 (0.0-750.0)	0.0 (0.0-900.0)	0.90	0.09
Concomitant medications				
GC use, n (%)	62 (55.9)	63 (56.7)	0.89	0.02
GC dose, mg/day, median (IQR)	2.5 (0.0-5.0)	2.5 (0.0-5.0)	0.74	0.04
MTX use, n (%)	86 (77.5)	82 (73.9)	0.53	0.08
MTX dose, mg/week, median (IQR)	8.0 (4.0-8.0)	6.0 (0.0-10.0)	0.69	0.06
b/tsDMARDs, n (%)	29 (26.1)	32 (28.9)	0.65	0.06

TNF-α inhibitors *	15 (13.5)	14 (12.6)	0.84	0.03
IL-6 inhibitors †	9 (8.1)	9 (8.1)	1.00	0.00
Abatacept	6 (5.4)	10 (9.0)	0.30	0.14
JAK inhibitors ‡	0 (0.0)	0 (0.0)	NA	NA
Rituximab	0 (0.0)	1 (0.0)	0.32	0.13
Tacrolimus, n (%)	13 (11.7)	14 (12.6)	0.84	0.03
Iguratimod, n (%)	5 (4.5)	3 (2.7)	0.47	0.10
Lymphocytopenia (<1000 /μL), n (%)	17 (15.3)	17 (15.3)	1.00	0.00
CDAI, median (IQR)	14.0 (10.5-24.9)	16.0 (12.1-23.8)	0.58	0.03
SDAI, median (IQR)	17.6 (11.8-26.9)	19.2 (13.2-24.2)	0.49	0.04

* TNF-α inhibitors were comprised of infliximab, adalimumab, etanercept, golimumab, and certolizumab pegol. † IL-6 inhibitors were comprised of tocilizumab and sarilumab. ‡ JAK inhibitors were comprised of baricitinib, filgotinib, peficitinib, tofacitinib, upadacitinib. Std.diff: standardized difference, Std.diff: standardized difference, IQR: interquartile range. SSZ: sulfasalazine, RF: rheumatoid factor, ACPA: anti-citrullinated peptide antibody, RA-LD: rheumatoid arthritis-associated lung disease, GC: glucocorticoid, MTX: methotrexate, bDMARDs: biological disease-modifying antirheumatic drugs, TNF: tumor necrosis factor, IL-6: interleukin-6, JAK: janus kinase, SDAI: the Simplified Disease Activity Index, CDAI: the Clinical Disease Activity Index.

Table 4. Effect of SSZ use on 1-year PCP incidence in overall Episodes (n=848)

	Univariable analysis		Multivariable analysis	
Clinical factors	**RR (95%CI)**	**P value**	**RR (95%CI)**	**P value**
Age	1.06 (1.02-1.10)	0.003	1.06 (1.02-1.10)	0.002
Female gender	8.63 (0.50-142)	0.13	8.07 (1.17-753)	0.013
RA-LD	3.36 (1.35-8.40)	0.01		
DM	4.21 (1.68-10.51)	0.002	4.27 (1.62-10.24)	0.005
SSZ use	0.09 (0.01-1.42)	0.09	0.05 (0.00-0.34)	0.0003
MTX use	1.02 (0.36-2.88)	0.97		
b/tsDMARDs use	1.22 (0.53-2.81)	0.65		
GC dose	1.06 (1.03-1.09)	0.0002	1.07 (1.03-1.10)	<0.0001

PCP: pneumocystis pneumonia, RA-LD: rheumatoid arthritis-associated lung disease, DM: diabetes mellitus, SSZ: sulfasalaizine, MTX: methotrexate, b/tsDMARDs: biological or targeted synthetic disease-modifying antirheumatic drugs, GC: glucocorticoid, RR: rate ratio, CI: confidence interval.

Table 5. Incidence of adverse events due to SSZ

	Number of events*	Incidence rate (95%CI) ‡
Adverse events	45	4.34 (3.26-5.78)
Skin rash	16	1.54 (0.95-2.51)
Gastrointestinal problems	12	1.16 (0.66-2.03)
Elevated liver transaminases	5	0.48 (0.20-1.16)
Malaise	2	0.19 (0.05-0.77)
Leukocytopenia	1	0.10 (0.01-0.68)
Thrombocytopenia	1	0.10 (0.01-0.68)
Drug-induced hypersensitivity syndrome	1	0.10 (0.01-0.68)
Others †	7	0.67 (0.32-1.41)

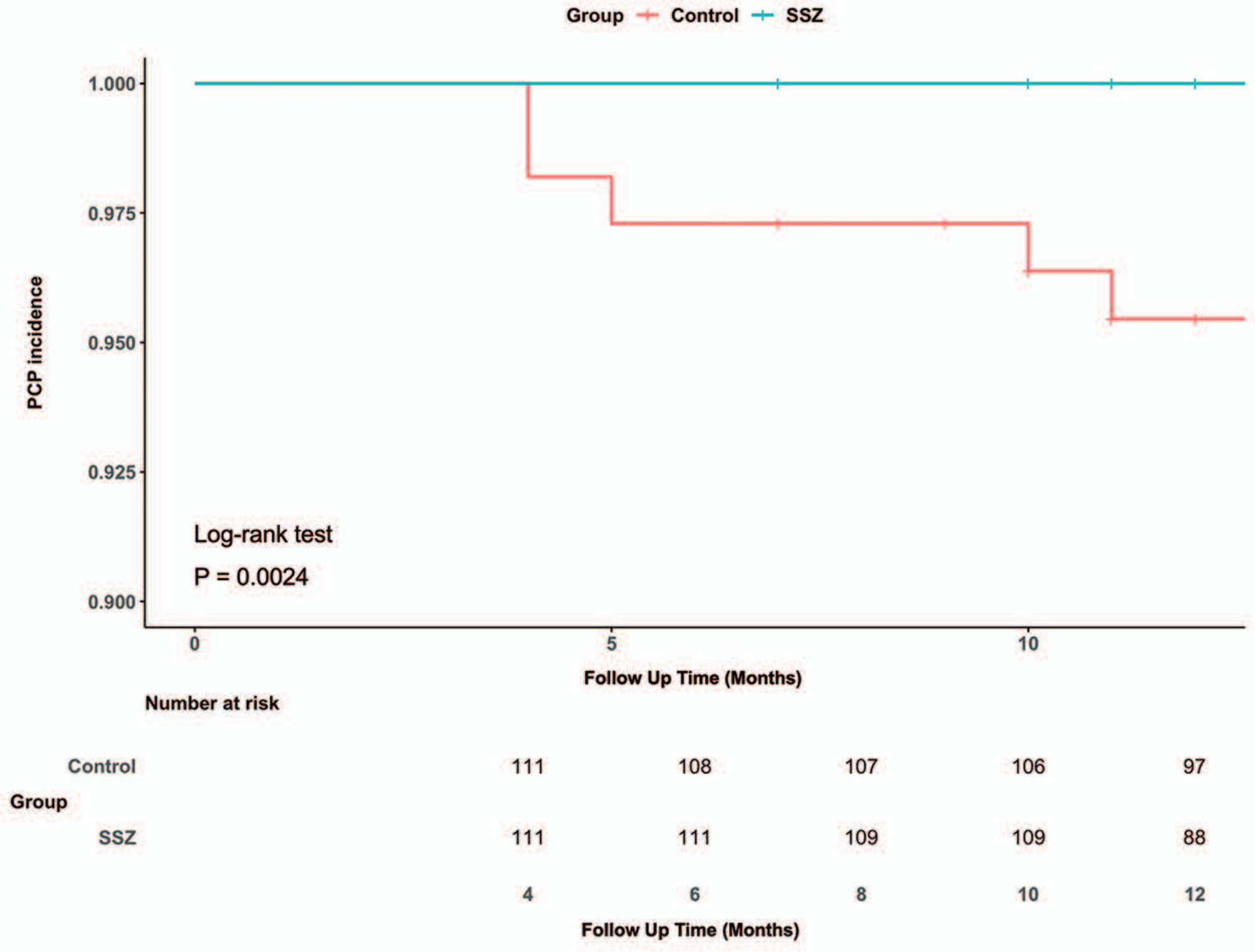
* Total follow-up period was 1036.5 person-years for 233 cases, † Including taste abnormality (2), fever (2), palpitations (1), arthralgia (1), elevated serum creatine kinase (1), ‡ Rate per 100 person-years. SSZ: sulfasalazine, CI: confidence interval.

FIGURE LEGENDS

Figure 1. Kaplan–Meier curve showing PCP-free survival in the propensity score -matched population.

PCP occurrence was compared between the SSZ and control groups adjusted for unbalanced baseline covariates with one-to-one propensity score matching using nearest neighbor matching with a caliper of 0.20.

PCP: Pneumocystis pneumonia; SSZ: Sulfasalazine


Group Control SSZ
1.000
0.975
0.950
0.925
0.900
PCP incidence
Log-rank test
P = 0.0024
0
5
10
Follow Up Time (Months)
Number at risk
Control 111 108 107 106 97
Group
SSZ 111 111 109 109 88
4 6 8 10 12
Follow Up Time (Months)