

Risk-benefit analysis of isoniazid monotherapy to prevent tuberculosis in patients with rheumatic diseases exposed to prolonged, high-dose glucocorticoids

Jun Won Park

Division of Rheumatology, Department of Internal Medicine, Seoul National University College of Medicine

Jeffrey R Curtis

University of Alabama at Birmingham

Hajeong Lee

Seoul National University College of Medicine

Jung-Kyu Lee

Seoul National University Seoul Metropolitan Government Boramae Medical Center

Yeong Wook Song

Seoul National University College of Medicine

Eun Bong Lee (✉ leb7616@snu.ac.kr)

Seoul National University College of Medicine <https://orcid.org/0000-0003-0703-1208>

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Abstract

Objective To investigate the incidence of tuberculosis (TB) in patients with rheumatic diseases receiving high-dose glucocorticoids and to evaluate the preventive effect of isoniazid (INH).

Methods This study included 1618 treatment episodes of prolonged (≥ 4 weeks), high-dose steroids (≥ 30 mg/day of prednisone) in 1160 patients. Of these, INH was administered in 152 (9.4%) treatment episodes (INH group), while others received no prophylaxis (control group). The high-risk subgroup ($n=92$) was defined as patients with 1) incomplete adherence to treatment of previous TB, 2) positive interferon- γ release assay, and/or 3) linear/reticular fibrotic lesions on chest radiographs. Primary outcome was 1-year incidence of TB in each group.

Results During 1579.8 person-years, 21 cases of TB occurred. The high-risk subgroup showed a significantly higher TB incidence than the non-high-risk subgroup (Incidence rate ratio=8.29). INH did not significantly affect the 1-year TB incidence in the whole population but numerically reduced it only in the high-risk subgroup [adjusted hazards ratio=0.48 (95% CI, 0.003–5.46)]. The incidence of adverse drug reactions (ADRs) related to INH was 111.6 (89.3–137.9)/100 person-years, including one fatal occurrence of fulminant hepatitis. The number needed to treat (NNT) to prevent one case of TB was lower than the number needed to harm (NNH) for one case of serious ADR only in the high-risk subgroup (3 vs. 11).

Conclusion INH treatment to prevent TB might be effective in high-risk patients but has a risk of frequent ADRs, which limits its use in general practice in patients not at a high risk of developing TB.

Background

Tuberculosis (TB) caused by *Mycobacterium tuberculosis* is an important healthcare problem globally. In 2016, 6.3 million new cases of TB and 1.3 million cases of TB-related death were reported among human immunodeficiency virus (HIV)-negative patients [1]. Although its incidence has been slowly decreasing since 2002, it is still a significant co-morbidity in patients with rheumatic diseases because the immunosuppressive agents used to treat rheumatic diseases increase the risk of TB [2]. Among the various immunosuppressive agents, high-dose glucocorticoids, a mainstay of the treatment of many rheumatic diseases, are particularly known to increase the TB risk [3]. However, because there have been no studies investigating the incidence of TB disease in such populations, it remains uncertain whether testing for latent tuberculosis infection (LTBI) and/or prophylactic treatment could be beneficial, especially in patients not being treated with tumour necrosis factor inhibitor (TNFi) or Janus kinase inhibitors (JAKi), where routine TB screening is recommended [4, 5]. Furthermore, previous studies that investigated the efficacy of isoniazid (INH) prophylaxis in high-dose steroid users included a small number of patients and showed inconsistent results [6, 7]. Therefore, most national guidelines for TB prophylaxis, especially those relevant to rheumatic disease patients, do not thoroughly address this issue, which has led to highly variable practice among rheumatologists regarding the diagnosis and treatment of LTBI in patients with rheumatic diseases receiving high-dose steroids [8, 9].

To address this problem, we investigated the incidence of TB and its risk factors in a large, single-centre cohort of patients with rheumatic diseases who underwent prolonged high-dose steroid treatment. In addition, we also analysed the efficacy and safety of prophylactic INH monotherapy, so that we could conduct a precise risk-benefit assessment of this strategy in both high-risk and non-high-risk patients.

Methods

The incidence of TB and strategy for LTBI detection in South Korea

The incidence of TB in South Korea was 96 per 100,000 person-years in 2005 and decreased to 77 per 100,000 person-years in 2016. Bacillus Calmette-Guérin (BCG) vaccination at birth has been mandatory since 1965, and the rate of vaccination in children under 3 years was 65.7% in 1990 and 99.8% in 2013. In the 7th Korean National Health and Nutrition Examination Survey in 2016, the prevalence of LTBI was 33.2% [95% confidence interval (CI), 30.9–35.6] [10, 11].

Interferon- γ release assays (IGRAs) have been used to screen for LTBI at our institution since 2009. A recent revised national guideline for TB in South Korea recommends IGRA alone or an IGRA plus tuberculosis skin test (TST) for the diagnosis of LTBI in immunosuppressed patients. However, TST alone is not recommended due to its low specificity in BCG-vaccinated patients. Of note, this guideline does not address the risk of developing TB or the need for LTBI evaluation in patients with rheumatic diseases receiving high-dose steroids [12].

Patients and clinical data

First, we captured clinical situations in which patients with a rheumatic disease were treated with high-dose glucocorticoids for more than 4 consecutive weeks (defined as a treatment episode) between January 2004 and December 2017 from the electronic medical database at Seoul National University Hospital. High-dose glucocorticoid treatment was defined as ≥ 30 mg/day of prednisone or equivalent [13]. The medical classifications used for case identification of rheumatic diseases according to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) are listed in the online supplementary text. Patients younger than 18 or with a history of HIV infection, current cancer, solid organ transplantation, or active TB disease requiring treatment at the start of high-dose glucocorticoids were excluded. Patients who concomitantly received TNFi during the observation period were also excluded. All captured treatment episodes were then divided into two groups (INH and control groups) according to whether a patient received INH with the high-dose steroid treatment.

The baseline date was defined as the first day of starting INH (in the INH group) or high-dose steroids (in the control group). Each patient remained on high-dose steroids for at least 4 weeks after the baseline date. The observation period for each treatment episode was 1 year from the baseline date unless TB disease or censoring events (death or loss to follow-up, defined as no follow-up visits for longer than 12 weeks from the previous hospital visit) occurred. Therefore, the study could include multiple treatment

episodes from single patients if they re-started prolonged high-dose steroid treatment more than 1 year after the relevant baseline date. The definition and observation of treatment episodes are described in Supplementary Fig. 1.

Demographic and clinical features at baseline, such as the initial steroid dose, concomitant immunosuppressant treatment, lymphocyte count, and chest radiographs, were collected. Data regarding the cumulative glucocorticoid dose during the 6 months prior to the baseline date were also collected. High-risk treatment episodes (High-risk subgroup) were defined as those with at least one of the following clinical factors at baseline; 1) incomplete adherence to treatment of previous TB infection, 2) a positive IGRA result, and 3) linear or reticular fibrotic lesions on chest radiographs, a pattern that is consistent with old TB lesion [14, 15].

The primary outcome was the 1-year incidence of TB in each group. The secondary outcome was the incidence of adverse drug reactions (ADRs) related to INH therapy. All potential ADRs in the INH group were reviewed and assigned a causality based on the chronology, known patterns of adverse effects associated with INH, and known effects of INH withdrawal [16]. Events with a probable/likely or certain causality were ultimately defined as ADRs in this study. The severity of ADRs was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. This study was carried out in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Seoul National University Hospital. Patient consent was waived due to the retrospective nature of the study.

Detection of TB

TB was diagnosed when a patient had both clinical and microbiological evidence of TB. To detect all cases of TB, data relating to acid-fast bacilli (AFB) staining/culture and TB polymerase chain reaction (PCR) from the included patients were reviewed. If a patient showed a positive result in at least one of the above tests, his or her medical records were reviewed to ascertain whether he or she had clinical features suggesting TB disease, and if so, anti-tuberculosis treatment was administered. A positive TB PCR result in the absence of clinical evidence of TB was not considered a true case of TB.

Isoniazid treatment to prevent TB

Because of the lack of universal recommendations regarding the evaluation of LTBI in patients with rheumatic diseases receiving high-dose steroids, TST and/or IGRA were not routinely performed during the observation period. Therefore, the selection of patients who would be treated with isoniazid was at the discretion of the treating physician and mainly based on the underlying disease, the initial steroid dose, and concomitant immunosuppressant treatment. Patients who received prophylactic treatment received 6 mg/kg INH (up to a maximum dose of 300 mg) once a day with pyridoxine replacement. There were no treatment episodes in which rifampicin or the combination of INH plus rifampicin was used for prophylaxis.

Statistical analysis

Continuous or dichotomous baseline data were compared using Student's t-tests or Chi-square tests, as appropriate. The incidence of TB between the two groups was compared using Poisson regression. The influence of clinical factors, including prophylactic INH, on outcome was analysed using the Cox proportional hazards model. The hazards ratio (HR) was adjusted for clinical factors that showed a relevant association ($P < 0.1$) with outcome in univariable analyses. The multivariable model was further adjusted for intra-cluster correlations using grouped sandwich variance estimates because some patients contributed multiple treatment episodes. If an outcome variable showed a complete separation between the two groups, Firth's penalized maximum likelihood was used for analysis [17]. All statistical analyses were performed using R V.3.3.1 software, and a P-value < 0.05 was considered statistically significant.

Results

Baseline characteristics

A total of 1618 treatment episodes from 1160 patients were analysed in this study. Prophylactic INH was administered with high-dose glucocorticoids in 152 (9.4%) treatment episodes, for a mean (SD) duration of 185 (153) days. In the INH group, INH was started along with high-dose steroids in most cases (149/152, 98.0%). In the remaining three treatment episodes, INH was delayed for 3–4 weeks. However, no incidences of TB occurred during the delay. The schema for inclusion in this study is shown in Supplementary Fig. 2.

The baseline characteristics of the patients are presented in Table 1. Briefly, patients in the INH group were older (45.1 vs. 42.1 years) and were more likely to have systemic lupus erythematosus (SLE) or microscopic polyangiitis as their underlying disease. By contrast, the proportion of patients with rheumatoid arthritis (RA; 1.3% vs. 4.8%) or Behcet disease (2.0% vs. 13.3%) was significantly lower in the INH group. In addition, more patients in the INH group concomitantly received oral cyclophosphamide, cyclophosphamide pulse therapy (intravenous), or steroid pulse therapy compared with the control group. The mean daily steroid dose (based on prednisone) that patients received during the 6 months prior to the baseline date was also higher in the INH group (9.9 vs. 12.6 mg/day), which suggests that the patients in the INH group were more immunosuppressed.

Among the entire population, the number of patients with a history of incomplete treatment for previous TB infection was 22 (1.4%). IGRA was performed at baseline in 187 (11.6%) treatment episodes, with a positive rate of 8.6% (16/187). Among the 1498 (92.6%) treatment episodes with available chest radiographs at baseline, 65 (4.3%) showed linear or reticular fibrotic lesions on chest radiographs. Finally, the number of patients in the high-risk subgroup was 92 (5.7%), and 16 (17.4%) received prophylactic INH.

Table 1

Baseline^a characteristics of the treatment episodes (n = 1618)

(n = number of treatment episodes)	Control group (n = 1466)	INH group (n = 152)	P-value
Age, year, mean (SD)	42.1 (15.5)	45.1 (17.1)	0.040
Male sex, n (%)	442 (30.2)	50 (32.9)	0.484
Disease duration, year, mean (SD)	3.2 (4.1)	2.0 (3.2)	< 0.001
Underlying diseases, n (%)			
Systemic lupus erythematosus, n (%)	714 (48.7)	86 (56.6)	0.065
Systemic sclerosis, n (%)	33 (2.3)	2 (1.3)	0.451
Dermatomyositis, n (%)	131 (8.9)	20 (13.2)	0.089
Polymyositis, n (%)	71 (4.8)	3 (2.0)	0.107
GPA, n (%)	34 (3.7)	5 (3.3)	0.805
MPA, n (%)	13 (0.9)	8 (5.3)	< 0.001
EGPA, n (%)	45 (3.1)	7 (4.6)	0.307
Polyarteritis nodosa, n (%)	26 (1.8)	4 (2.6)	0.455
Rheumatoid arthritis, n (%)	70 (4.8)	2 (1.3)	0.049
Adult-onset Still's disease, n (%)	39 (2.7)	3 (2.0)	0.612
Behcet's disease, n (%)	195 (33.3)	3 (2.0)	< 0.001
IGRA, interferon- γ release assay; INH, isoniazid; LTBI, latent tuberculosis infection; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; EGPA, eosinophilic granulomatosis with polyangiitis; PD, prednisone; SD, standard deviation.			
^a The baseline date was defined as the day on which INH prophylaxis (INH group) or high-dose steroids (control group) were started.			
^b Including polymyalgia rheumatica, Takayasu's arteritis, temporal arteritis, and relapsing polychondritis.			
^c Including an incomplete adherence to treatment of previous TB infection, a positive IGRA result, and/or the presence of linear or reticular fibrotic lesions on chest radiographs.			
^d Based on the dose of prednisone.			

(n = number of treatment episodes)	Control group (n = 1466)	INH group (n = 152)	P-value
Primary Sjogren's syndrome, n (%)	8 (0.5)	1 (0.7)	0.859
Others, n (%) ^b	54 (3.7)	7 (4.6)	0.570
High-risk for LTBI, n (%) ^c	76 (5.2)	16 (10.5)	0.007
Incomplete adherence to treatment of previous TB infection	19/1466 (1.3)	3/152 (2.0)	0.492
Positive IGRA result	12/161 (7.5)	4/26 (15.4)	0.063
Linear or reticular fibrotic lesions on chest radiographs	56/1350 (4.1)	9/148 (6.1)	0.273
Steroid pulse treatment, n (%)	226 (15.4)	59 (38.8)	< 0.001
Oral cyclophosphamide, n (%)	65 (4.4)	19 (12.5)	< 0.001
Cyclophosphamide pulse treatment, n (%)	130 (8.9)	34 (22.4)	< 0.001
Mean steroid dose used during the prior 6 months, mg/day, mean (SD) ^d	9.9 (10.0)	12.6 (9.5)	0.002
Baseline lymphopenia, n (%) ^e	335 (22.9)	57 (37.5)	< 0.001
IGRA, interferon- γ release assay; INH, isoniazid; LTBI, latent tuberculosis infection; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; EGPA, eosinophilic granulomatosis with polyangiitis; PD, prednisone; SD, standard deviation.			
^a The baseline date was defined as the day on which INH prophylaxis (INH group) or high-dose steroids (control group) were started.			
^b Including polymyalgia rheumatica, Takayasu's arteritis, temporal arteritis, and relapsing polychondritis.			
^c Including an incomplete adherence to treatment of previous TB infection, a positive IGRA result, and/or the presence of linear or reticular fibrotic lesions on chest radiographs.			
^d Based on the dose of prednisone.			

^e Defined as < 800 lymphocytes per microliter.

Incidence of TB disease and its risk factors

During 1579.8 person-years of observation, 21 cases of TB occurred, for an incidence of 13.3 (95% CI, 8.2–20.3) per 1000 person-years. The clinical features of the 21 cases at baseline and at the time of TB occurrence are summarized in Supplementary Tables 1 and 2, respectively. SLE was the most frequent underlying rheumatic disease in the patients who developed TB disease (15/21, 71.4%), and the mean duration between the baseline date and the diagnosis of TB was 131.9 (92.2) days. Fifteen patients (71.4%) had pulmonary TB. Extrapulmonary involvement and miliary TB occurred in seven (33.3%) and four (19.0%) patients, respectively. There were four cases of multidrug-resistant TB. In the other cases, 14 (66.7%) patients were initially treated with the standard combination regimen of INH, rifampicin, ethambutol, and pyrazinamide (Supplementary Table 2).

The incidence (per 1000 person-years) of TB in the high-risk subgroup was significantly higher than that in the non-high-risk subgroup [82.5 (seven cases/84.9 person-years) vs. 9.3 (14 cases/1495.0 person-years)] (Fig. 1). Univariable Cox analysis also showed that presence in the high-risk subgroup was the most important risk factor associated with TB disease ([crude HR = 8.62 (95% CI, 3.48–21.35)]. In addition, underlying SLE, a higher mean steroid dose used during the 6 months prior to the baseline date, and concomitant steroid pulse treatment were also associated with increased risk of TB. However, the initial steroid dose and concomitant cyclophosphamide treatment were not associated with outcome. In the multivariable analysis, SLE, a higher mean steroid dose used during the 6 months prior to the baseline and presence in the high-risk subgroup were significantly associated with increased risk of TB (Table 2).

Table 2
Clinical factors associated with the 1-year TB incidence during the observation period

	Univariable analysis		Multivariable analysis ^a	
	HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
Age (per 5-year increment)	0.95 (0.82–1.10)	0.475	b	
Male sex	1.40 (0.51–3.82)	0.513	b	
Disease duration (per 5-year increment)	0.95 (0.55–1.64)	0.845	b	
SLE	2.54 (0.99–6.55)	0.054	3.78 (1.37–10.48)	0.011
High-risk subgroup	8.62 (3.48–21.35)	< 0.001	13.14 (4.72–36.56)	< 0.001
Initial steroid dose at baseline (\geq 60 mg/day of prednisone vs. a lower dose) ^c	0.92 (0.39–2.18)	0.924	b	
Concomitant oral cyclophosphamide	0.42 (0.003–3.04)	0.485	b	
Concomitant cyclophosphamide pulse	1.47 (0.43–5.00)	0.535	b	

CI, confidence interval; HR, hazard ratio; SLE, systemic lupus erythematosus; TB, tuberculosis.

^a Model included the clinical factors that showed a significant association ($P < 0.1$) in univariable analyses, and was adjusted for clustering.

^b Not included in the multivariable model as a covariate.

^c Dose was calculated after excluding the dose of the concomitant steroid pulse treatment.

^d Based on the dose of prednisone.

	Univariable analysis		Multivariable analysis ^a	
Concomitant steroid pulse	2.38 (0.96– 5.89)	0.061	1.98 (0.80– 4.91)	0.140
Mean steroid dose used during the prior 6 months, mg/day ^d	1.04 (1.01– 1.06))	0.007	1.04 (1.01– 1.08)	0.013
Baseline lymphopenia ^e	1.26 (0.49– 3.25)	0.632	b	
CI, confidence interval; HR, hazard ratio; SLE, systemic lupus erythematosus; TB, tuberculosis.				
^a Model included the clinical factors that showed a significant association ($P < 0.1$) in univariable analyses, and was adjusted for clustering.				
^b Not included in the multivariable model as a covariate.				
^c Dose was calculated after excluding the dose of the concomitant steroid pulse treatment.				
^d Based on the dose of prednisone.				

^e Defined as < 800 lymphocytes per microliter.

Prophylactic effectiveness of INH treatment

Two patients in the INH group developed TB, 72 and 169 days after the baseline date, respectively. The incidence of TB was 13.3 (19 cases/1431.0 person-years) in the control group and 13.4 (two cases/148.1 person-years) in the INH group, which was not a significant difference (Fig. 2). This result was consistent after adjusting for clinical factors associated with the 1-year incidence of TB disease [adjusted HR = 0.57 (0.12–2.71)].

The prophylactic effect of INH was further investigated after stratification of the treatment episode by the presence of high-risk factors at baseline. In the subgroup of patients without risk factors, INH treatment did not significantly influence the 1-year TB incidence [adjusted HR = 1.08 (0.22–5.38)]. In the high-risk subgroup, INH tended to reduce the risk of TB disease, but this difference was not statistically significant [adjusted HR = 0.48 (0.003–5.46)] (Table 3). A similar result was obtained when the Cox regression analysis was performed after excluding the three treatment episodes, in which the administration of prophylactic INH was delayed 3–4 weeks after the initiation of high-dose glucocorticoids (data not shown).

Table 3

The effect of prophylactic INH on the 1-year incidence of TB according to the presence of risk factors

	Non-high-risk subgroup (n = 1526)	High-risk subgroup (n = 92) ^a
Number of TB cases / Observation period in the control group	12 / 1362.2 person-years	7 / 69.5 person-years
Number of TB cases / Observation period in the INH group	2 / 132.7 person-years	0 / 13.5 person-years
Crude hazards ratio of the INH group (95% CI)	0.76 (0.38–7.62)	0.31 (0.002–2.46)
Adjusted hazards ratio of the INH group (95% profile likelihood CI)	1.08 (0.22–5.38) ^b	0.48 (0.003–5.46) ^c
CI, confidence interval; INH, isoniazid; TB, tuberculosis.		
^a Firth penalized maximum likelihood was used due to complete separation of outcome.		
^b Included concomitant steroid pulse and cumulative steroid dose as covariates, and was also adjusted for clustering.		
^c Included age, male sex, and mean steroid dose used during the prior 6 months as covariates, and was also adjusted for clustering.		

Safety of INH treatment

During a total of 77.0 person-years of observation in the INH group, 86 ADRs occurred in the 68 treatment episodes, with an incidence of 111.6 (89.3–137.9) per 100 person-years (Table 4). Most ADRs were of mild-to-moderate severity, and 25 patients (36.8%) discontinued INH treatment. Increased serum transaminase was the most common ADR [50.6 (36.0–69.2)/100 person-years], followed by peripheral neuropathy [33.8 (22.1–49.5)/100 person-years] and gastrointestinal discomfort [13.0 (6.2–23.9)/100 person-years]. There was one case of fulminant hepatitis in a patient in the high-risk subgroup, and the patient ultimately expired due to progression to liver failure.

Table 4
The incidence of adverse drug reactions caused by prophylactic INH

	Number of cases ^a	Incidence rate (95% CI) ^b
Mild-to-moderate adverse drug reactions	85	110.4 (88.2 to 136.5)
LFT abnormality	31	40.3 (27.4 to 57.2)
Peripheral neuropathy	26	33.8 (22.1 to 49.5)
GI discomfort	10	13.0 (6.2 to 23.9)
Skin rash	6	7.8 (2.9 to 17.0)
Thrombocytopenia	5	6.5 (2.1 to 15.2)
Anaemia	1	1.3 (0.03 to 7.2)
Leukopenia	1	1.3 (0.03 to 7.2)
Anorexia	2	2.6 (0.3 to 9.4)
Others ^c	3	3.9 (0.8 to 11.4)
Serious adverse drug reactions ^d	1	1.3 (0.03 to 7.2)
Fulminant hepatitis	1	1.3 (0.03 to 7.2)
CI, confidence interval; GI, gastrointestinal; INH, isoniazid; LFT, liver function test; NA, not applicable.		
^a The total observation period was 77.0 person-years for 152 episodes.		
^b Rate per 100 person-years.		
^c Including eosinophilia (n = 1), pruritus (n = 1), and general weakness (n = 1).		
^d Occurred in the high-risk subgroup.		

Risk-benefit assessment of INH treatment

In the entire patient population, the number needed to treat (NNT) to prevent one case of TB was a negative value because the crude incidence rate was slightly higher in the INH group. The number needed to harm (NNH) to cause one ADR of any severity was 2 (1.6–2.1), and the NNH to cause one serious ADR was 152 (51.5–∞). In the high-risk subgroup, the corresponding NNT was 11 (6.4–36.9), whereas the NNHs to cause any ADR or any serious ADR were 2 (1.3–3.9) and 16 (5.5–∞), respectively. By contrast, in the non-high-risk group, the NNT was negative, while the NNH for any ADR was 3 (1.9–2.8).

Discussion

Systemic glucocorticoid therapy is an important treatment option for many rheumatic diseases, but it is also a major cause of opportunistic infections, including TB [3, 18, 19]. However, there have been few epidemiologic reports investigating the incidence of LTBI or providing a risk-benefit assessment for TB prophylaxis in patients with rheumatic diseases receiving high-dose steroids.

In the present study, the incidence of TB in patients with rheumatic diseases receiving prolonged, high-dose steroids was 13.3 (8.2–20.3) per 1000 person-years, which was significantly higher than that of the general population in South Korea (0.77 per 1000 person-years in 2016) [10]. This result is consistent with previous reports suggesting that impaired cellular immunity caused by steroid treatment significantly increases the risk of TB [7, 20]. However, INH treatment to prevent TB did not reduce its 1-year incidence, contrary to its proven efficacy in HIV-positive or transplant patients [21–24].

In this study, presence in the high-risk subgroup, defined by incomplete adherence to treatment of previous TB infection, a positive IGRA result, and/or radiographic evidence of previous pulmonary TB, was the most important risk factor for TB, which suggests that reactivation of latent TB is a major cause of overt TB. Although current guidelines suggest that evaluation for LTBI by IGRA and/or TST before high-dose glucocorticoid treatment be considered, this is not based on robust evidence [9, 12]. There was, therefore, limited evaluation for LTBI in our study population. Furthermore, the diagnostic utility of TST in such patients is limited, because its sensitivity and specificity are significantly influenced by previous steroid use and BCG vaccination [25–27]. Although some studies reported the superior specificity of IGRA compared with TST, its diagnostic performance can also be impaired in patients receiving steroid treatment [28–31]. Therefore, defining the patient group in which prophylactic INH treatment could be beneficial should be based on a comprehensive evaluation consisting of careful evaluation of patient history, chest radiographs, and laboratory tests. In fact, the 1-year incidence of TB was similar in the control and INH groups, suggesting that non-selective application of INH treatment in the study population was not effective in preventing TB. By contrast, a subgroup analysis performed in the high-risk subgroup showed that INH treatment numerically reduced the 1-year incidence of TB. However, since the number of patients in this subgroup was small, the efficacy of INH prophylaxis in this population should be re-evaluated in future larger studies.

To determine whether prophylactic INH treatment is beneficial to patients, its safety profile is also an important consideration. In this context, it is of note that INH treatment was associated with frequent ADRs (including one fatal case of hepatitis), which resulted in a high discontinuation rate. A risk-benefit analysis also showed that the NNT for INH treatment was much greater than the NNH, suggesting low benefit. Therefore, non-selective application of INH prophylaxis in patients with rheumatic diseases receiving prolonged high-dose steroids results in a high risk of adverse events, outweighing its potential benefit. By contrast, the NNT in the high-risk subgroup was slightly lower than the risk of serious ADRs, emphasizing again that INH prophylaxis should be considered only in this population.

This study has some limitations. First, the number of patients in the high-risk subgroup was small, and the screening criteria used to define this subgroup (e.g., IGRA testing) was not uniformly performed in the

whole population, which reduces the statistical power of the study. Therefore, the prophylactic effectiveness of INH treatment should be further evaluated in future large-scale studies in which all included patients undergo IGRA and have at least one high-risk factor. However, our result could be an important basis for establishing clinical guidelines in resource-limited countries where routine IGRA testing is not available. Second, South Korea is a country of intermediate TB burden, so our results may not be applicable to other countries with different TB burdens, although our finding of minimal or no benefit in non-high-risk patients is presumably generalizable. Finally, mean duration of INH administration in the INH group was approximately 6 months, which was shorter than recommended for the treatment of LTBI. Therefore, prophylactic effect of INH could be underestimated in this study [32].

Conclusion

In conclusion, this study showed the incidence of TB and the prophylactic effect of INH treatment in patients with rheumatic diseases receiving prolonged, high-dose glucocorticoid treatment. INH treatment to prevent TB might be effective in high-risk patients. However, the high incidence of ADRs limits its utility in non-high-risk patients.

Abbreviations

ADR, adverse drug reaction; AFB, acid-fast bacilli; BCG, Bacillus Calmette-Guérin; CI, confidence interval; HIV, human immunodeficiency virus; HR, hazards ratio; IGRA, Interferon- γ release assay; INH, isoniazid; JAKi, Janus kinase inhibitors; LTBI, latent tuberculosis infection; NNH, number needed to harm; NNT, number needed to treat; PCR, polymerase chain reaction; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; TB, tuberculosis; TNFi, tumour necrosis factor inhibitor; TST, tuberculosis skin test;

Declarations

Ethical approval and consent to participate

The study was carried out in accordance with the Declaration of Helsinki, and was approved by the institutional review board (IRB) of Seoul National University Hospital [IRB No 1508-050-694]. Consent was waived by the IRB because of the retrospective nature of the study.

Consent for publication

Not applicable

Availability of data and material

All of the data supporting the conclusions of this article are included within the article.

Competing interests

Jeffrey R Curtis reported grants and personal fees from Abbvie, grants and personal fees from Amgen, grants and personal fees from BMS, grants and personal fees from Corrona, grants and personal fees from Eli Lilly, grants and personal fees from Janssen, grants and personal fees from Myriad, grants and personal fees from Pfizer, grants and personal fees from Regeneron, grants and personal fees from Roche, grants and personal fees from UCB, during the conduct of the study. The other authors declare that they have no conflicts of interest.

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Author's contributions

EBL and JWP were responsible for the study design. All the authors were responsible for the acquisition, analysis, or interpretation of the data. JWP drafted the manuscript and performed the statistical analysis. All the authors were responsible for critical revision of the manuscript. EBL supervised the study.

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Figures

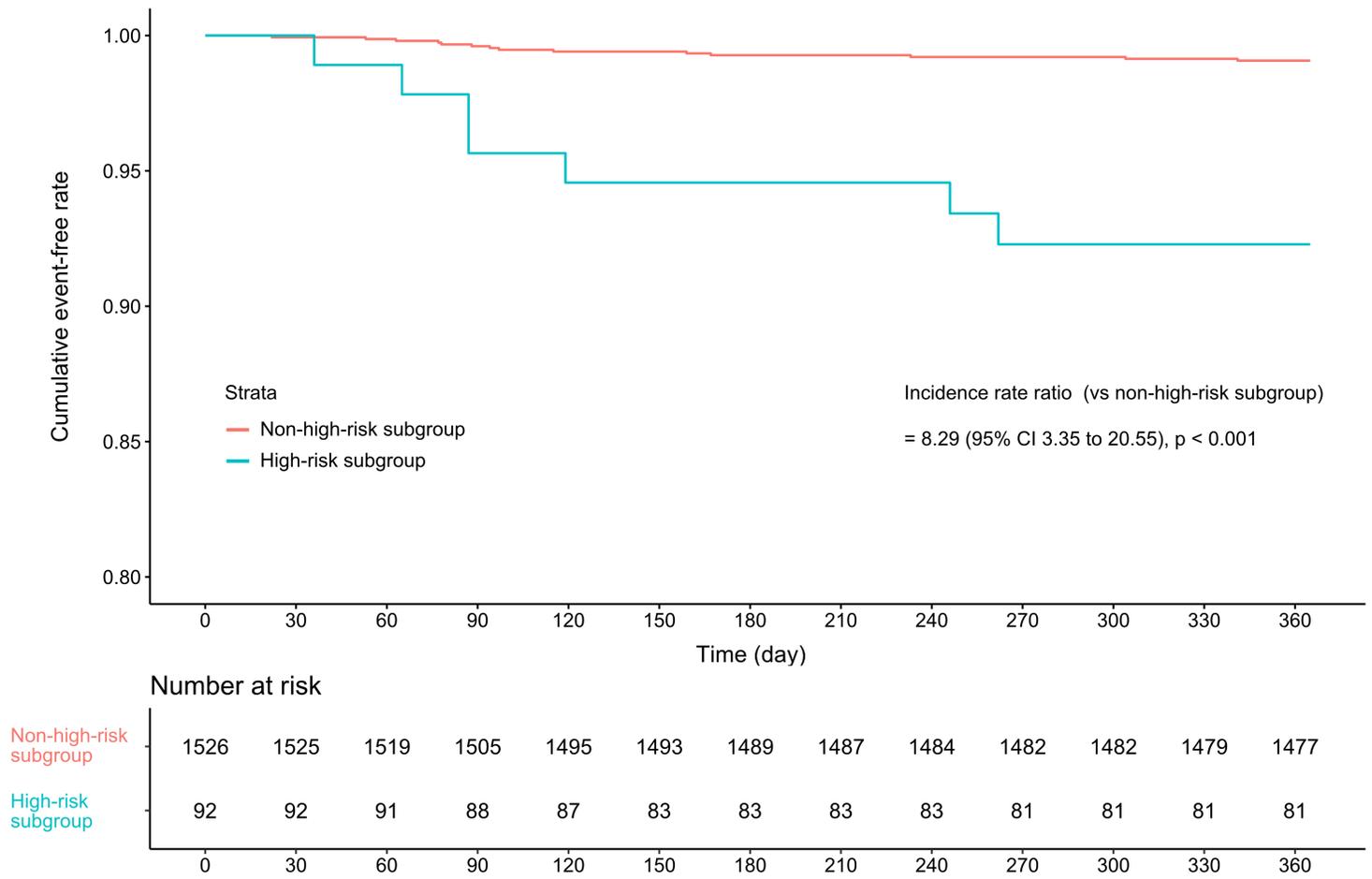


Figure 1

Kaplan–Meier curves indicating the 1-year tuberculosis incidence according to the presence of high-risk factors.

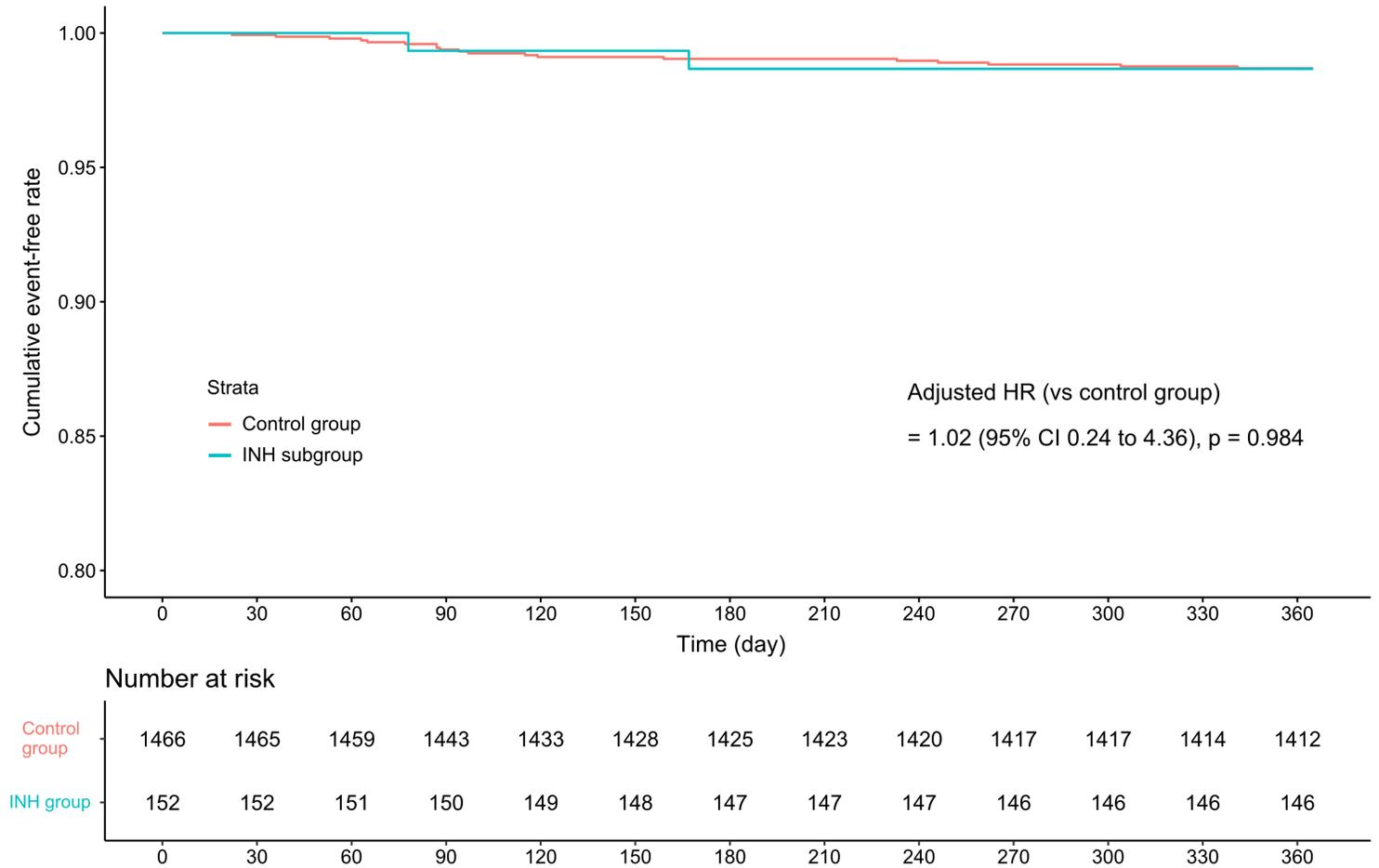


Figure 2

Kaplan–Meier curves indicating the 1-year tuberculosis incidence in the control and INH groups.

Supplementary Files

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