Tuberculosis in Systemic Lupus Erythematosus in an Endemic Area and the Role of Isoniazid Prophylaxis During Corticosteroid Therapy

MO YIN MOK, YI LO, TAK MAO CHAN, WOON SING WONG, and CHAK SING LAU

ABSTRACT. ***Objective.*** The efficacy of isoniazid (INAH) prophylaxis against tuberculosis (TB) in patients taking corticosteroid remains controversial. Hong Kong is an endemic area for TB, with an annual risk of 0.11/100 in the general population. Patients with systemic lupus erythematosus (SLE) have an increased susceptibility to TB because of their intrinsic immunocompromised state and the use of corticosteroid therapy. We examined the usefulness of INAH in the prevention of recurrences of TB in patients with SLE receiving high dose corticosteroid therapy.

Methods. Medical records of a cohort of patients with SLE were reviewed. Patients with a history of TB who had previously been adequately treated were retrospectively examined for subsequent recurrence of TB. A comparison was performed based on the use of INAH at the discretion of the attending physician in some patients (INAH group) but not others (non-INAH group) during lupus exacerbation that required the use of prednisolone ≥ 15 mg/day or equivalent.

Results. A total of 91 episodes of TB from 76 individuals in a cohort of 652 SLE patients with a duration of followup of 13.9 ± 7.5 years were identified (prevalence of 1.06/100 patient-years). 43 episodes were given INAH while 48 were not. There were 18 recurrences of TB (recurrence rate of 1.66/100 patient-years). Recurrence rates in the INAH and non-INAH groups were 1.59 and 1.74 per 100 patient-years (p = 0.72). However, patients in the INAH group had more lupus exacerbations. Further, extrapulmonary TB was also found to have a higher recurrence rate than pulmonary TB. A case-controlled analysis was thus performed (n = 46) matching patients for the number of lupus exacerbations, cumulative doses of prednisolone, and initial site of TB. There was no difference in the recurrence rates of TB between the matched INAH (0.55/100 patient-years) and non-INAH (1.04/100 patient-years) groups (p = 0.66).

Conclusion. Patients with SLE have a higher prevalence of TB infection than the general population. They are at risk of TB recurrence when given immunosuppressive doses of corticosteroid. (J Rheumatol 2005;32:609–15)

Key Indexing Terms:
CHEMOPROPHYLAXIS MYCOBACTERIAL INFECTION TUBERCULOSIS
CORTICOSTEROID SYSTEMIC LUPUS ERYTHEMATOSUS

Patients with impaired cell mediated immunity are susceptible to *Mycobacterium tuberculosis* infection, which may be disseminated and is associated with a high mortality[1]. Patients with symptomatic human immunodeficiency virus (HIV) infection[2] and those requiring immunosuppressive therapies, such as postrenal transplant patients, have been reported to be more susceptible to tuberculosis (TB)[3,4]. TB has also been increasingly reported in patients with rheumatoid arthritis (RA) receiving novel biologic agents including tumor necrosis factor-α (TNF-α) antagonists[5,6].

Chemoprophylaxis against TB has been shown to be efficacious and prolong the survival of HIV infected patients[7–9]. Posttreatment isoniazid (INAH) prophylaxis has also been shown to decrease the risk of recurrence of TB in HIV-positive individuals[10]. Guidelines on the use of chemoprophylaxis have been issued in managing these patients[11,12]. On the other hand, there is limited information in patients receiving corticosteroids and other immunosuppressants. The American Thoracic Society recommended the use of INAH in patients given corticosteroids at doses equivalent to prednisolone 15 mg or more per day if they have a positive response to the tuberculin skin test[13]. However, this issue was not addressed in the guidelines on management of TB published by the British Thoracic Society in 1998[14]. Further, the risk/benefit ratio of longterm TB chemoprophylaxis has not been determined. Isoniazid-induced hepatitis is a potential problem[15,16].

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Patients with systemic lupus erythematosus (SLE) have impaired cellular and humoral immune responses intrinsically. Concomitant use of corticosteroid and immunosuppressants further contributes to the immunocompromised state of these patients. We evaluated the usefulness of INAH in patients with SLE who had a history of TB and who required the use of immunosuppressive doses of corticosteroid to control their lupus disease activity in an area of high TB prevalence.

MATERIALS AND METHODS

Medical records of an inception cohort of patients with SLE as defined by the 1982 revised American College of Rheumatology classification criteria[17] from 1987 to 2001 were studied. Patients with a history of TB before and after the onset of SLE were identified. Clinical TB was verified by clinical and/or radiological findings plus a positive culture of *M. tuberculosis*, or a positive polymerase chain reaction (PCR) from body fluid or tissue, or the observation of caseating granuloma on histopathology. Radiological evidence of past TB was defined as the presence of pleural thickening and lung fibrosis or old cavitation in the upper lobe of the lungs. Patients were excluded if they had incomplete anti-TB treatment. Adequate treatment of TB was defined as full treatment for 1 year for pulmonary TB and ≥ 1.5 years for extrapulmonary TB. All patients were followed during the treatment period by chest physicians at the Department of Health under DOTS (Directly Observed Therapy Shortcourse)[18] to ensure compliance and treatment response.

Demographic data including age, sex, ethnicity, and duration and clinical manifestations of SLE were recorded. Records were also reviewed for concomitant conditions that may predispose these patients to TB, including diabetes mellitus, liver cirrhosis, chronic alcoholism defined as alcohol consumption > 20 and 15 units per week in men and women, respectively, and previous gastrectomy. Serological profiles including antinuclear antibody (ANA), anti-double stranded (ds) DNA antibody, and antiextractable nuclear antigen (ENA) antibody (anti-Sm, anti-Ro, anti-La, anti-RNP antibodies) status were ascertained. Disease activity was determined by the SLE Disease Activity Index (SLEDAI)[19] at each visit. Clinical relapse was defined as an increase in the patient's SLEDAI score by 6 points that required the augmentation of corticosteroid dose equivalent to prednisolone ≥ 15 mg per day. The number of clinical relapses and the use of therapeutic regimens including oral and pulse corticosteroid, cumulative dose of steroid used, and other immunosuppressants including azathioprine and cyclophosphamide were recorded.

Since there was no agreement on the indication of chemoprophylaxis, some patients were given INAH (INAH group) and others were not (non-INAH group), at the attending physicians' discretion whenever the lupus condition flared requiring the use of immunosuppressive doses of steroid (prednisolone dose ≥ 15 mg/day) and/or other immunosuppressive drugs. Patients in the INAH group were given INAH 300 mg and pyridoxine 10 mg daily for as long as immunosuppressive doses of corticosteroid were required. The clinical course of patients in the 2 groups was followed either up to the recurrence of TB or the time of study or 6 months after the cessation of INAH therapy. The rates of recurrence of TB per patient-year of followup between the 2 groups were compared.

As the rates of TB recurrences were subsequently found to be dependent on the initial site of TB involvement and that patients given INAH prophylaxis were found to have a higher rate of SLE flares and cumulative dose of corticosteroid use in the initial observational study, a 1:1 case-controlled study was performed matching patients with regard to number of flares of their SLE, cumulative dose of corticosteroid, and the initial site of TB involvement.

Statistical analysis. In the initial comparison study and the subsequent case-controlled study, the chi-square test was used to compare the number of recurrences of TB and the number of SLE relapses per patient-year of followup in the INAH and the non-INAH groups. A Mann-Whitney U test was used to compare the dosages of corticosteroid used between the 2 groups.

RESULTS

Demographic data and clinical manifestations of patients with SLE. There were 652 SLE patients in the cohort, with a mean duration of followup of 13.9 ± 7.5 years. Ninety-six episodes of TB were found in 81 patients, giving a prevalence of 1.06/100 patient-years.

There was one death from disseminated TB. Four patients were still receiving anti-TB treatment at the time of study. Therefore the clinical course of 76 patients in the cohort was followed for recurrence of TB. Table 1 shows the demographic and clinical characteristics of these patients. There were 69 women and 7 men. The mean ± SD (range) age of patients at the time of study was 46.6 ± 11.7 (22–81) years and the age at onset of SLE was 31.4 ± 11.7 (13–71) years. The mean duration of followup was 14.6 ± 7.3 (median 13.0, range 1–31) years.

Characteristics of TB infection in patients with SLE. Of the 76 patients, 19 developed clinical TB before the onset of

Table 1. Demographic and clinical characteristics of patients with SLE (n = 76).

	N (%)
Female:male	69:7
Age at study, yrs	46.6 ± 11.7*
Age at SLE diagnosis, yrs	31.4 ± 11.7*
Duration of followup for SLE, yrs	13.9 ± 7.5*
Clinical manifestations	
Polyarthralgia	65/76 (85.5)
Malar rash	54/76 (71.1)
Autoimmune hemolytic anemia	53/76 (69.7)
Leukopenia	46/76 (60.5)
Immune thrombocytopenia	40/76 (52.6)
Renal involvement	40/76 (52.6)
Discoid rash	31/76 (40.8)
Serositis	31/76 (40.8)
Photosensitivity	21/76 (27.6)
Oral ulceration	18/76 (23.7)
Neurological involvement	16/76 (21.1)
Secondary Sjögren's syndrome	13/76 (17.1)
Autoantibodies	
Antinuclear antibodies	80/76 (95.2)
Anti-Ro	50/76 (59.5)
Anti-RNP	14/76 (16.7)
Anti-La	11/76 (13.1)
Anti-Sm	8/76 (9.5)
Comorbidities	
Gastrectomy	1/76 (1.3)
Diabetes mellitus	1/76 (1.3)
Chronic alcoholism	0/76 (0)
Liver cirrhosis	0/76 (0)
Cumulative dose of immunosuppressants used (mg/patient-yr)	
Prednisolone	2502.5 ± 2727.7*
Azathioprine	5387.1 ± 7194.4*

* Results are expressed as mean ± SD.

SLE. Twelve patients developed concurrent TB at the onset of SLE. Forty-five patients developed TB at a median of 4.0 years after SLE was diagnosed. One patient had diabetes mellitus and one had partial gastrectomy. None of the 76 patients was a chronic alcoholic and none had liver cirrhosis.

There were a total of 91 episodes of TB in these 76 patients. Fifty-five episodes were pulmonary TB (55/91, 60.4%), while 36 episodes were extrapulmonary infections (36/91, 39.6%). Table 2 shows the sites of TB infection. Articular and soft tissue infection (8/36, 22.2%) was the most prevalent site of extrapulmonary involvement, followed by meningitis (6/36, 16.7%), miliary TB (6/36, 16.7%), lymphadenitis (5/36, 13.9%), osteomyelitis (3/36, 8.3%), kidney and urinary bladder infection (2/36, 5.6%), and endometritis (1/36, 2.6%). Disseminated infection occurred in 5 (13.9%) patients.

M. tuberculosis was identified by positive culture and PCR from body fluid or tissue biopsy in 83.5% (76/91) and 4.4% (12/91) of patients, respectively. *M. tuberculosis* was recovered from sputum (n = 46), pleural fluid (n = 8), bronchoalveolar lavage (n = 6), cerebrospinal fluid (n = 5), and urine (n = 1) and from tissue biopsies from lymph node (n = 7), synovium and soft tissues (n = 8), urinary bladder mucosa (n = 2), and endometrium (n = 1). Radiological findings of active pulmonary TB were also found in 5 (13.2%) patients.

INAH prophylaxis. Among the 91 episodes of TB analyzed, INAH was adopted in 43 episodes from 33 patients when they were started on immunosuppressive doses of corticosteroids, whereas in 48 episodes from 43 patients INAH was not given. In the INAH group, INAH 300 mg daily with pyridoxine supplement (10 mg daily) was used for as long as the dose of corticosteroid was prescribed at an equivalent dose of prednisolone ≥ 15 mg per day and restarted whenever the dosage of the prednisolone was > 15 mg per day. Table 3 shows the baseline characteristics of patients given INAH and those who were not. Patients given INAH were found not to differ from those who were not given INAH in terms of their clinical features, number of SLE flares prior to initiation of INAH therapy, cumulative corticosteroid use, and previous site of TB involvement at baseline. The mean duration of INAH use per episode of augmentation of prednisolone to ≥ 15 mg/day was 15.4 ± 12.2 (median 12.0) months. There was no report of intolerance or toxicity that led to discontinuation of INAH prophylaxis or problems with compliance.

Table 2. Characteristics of TB infection (n = 91).

Demographics	N (%)
Age of patient at diagnosis of TB, yrs	31.6 ± 11.3*
Occurrence from SLE onset, yrs	5.0 ± 5.0*
Site of TB involvement	
Pulmonary	55/91 (60.4)
Extrapulmonary	36/91 (39.6)
Articular and soft tissue infection	8/36 (22.2)
Miliary	6/36 (16.7)
Meningitis	6/36 (16.7)
Disseminated	5/36 (13.9)
Lymphadenitis	5/36 (13.9)
Osteomyelitis	3/36 (8.3)
Renal and urinary bladder infection	2/36 (5.6)
Endometritis	1/36 (2.6)
Diagnosis	
Positive growth of *M. tuberculosis*	76/91 (83.5)
Radiological and clinical features	12/91 (13.2)
Positive PCR	4/91 (4.4)

* Results are expressed as mean ± SD. PCR: polymerase chain reaction.

Rate of recurrence of TB. Eighteen recurrences of TB were found in these 76 patients after a mean followup time of 11.6 ± 6.8 years, giving a recurrence rate of 1.66 per 100 patient-years. These included 7 pulmonary and 11 extrapulmonary infections. Table 3 shows the pattern of recurrence of TB. Pulmonary TB usually recurred as pulmonary TB, whereas extrapulmonary TB recurred in extrapulmonary sites. Among the initial 55 episodes of pulmonary TB, 7 recurrences occurred, with 6 of these episodes recurring locally in the lungs. Only one patient who had initial pulmonary TB subsequently relapsed as disseminated TB. On the other hand, extrapulmonary TB showed a higher propensity for recurrence than pulmonary TB. There were 11 recurrences among the initial 36 episodes of extrapulmonary TB. These 11 episodes recurred as extrapulmonary involvement. The rates of TB recurrence in patients with previous pulmonary and extrapulmonary involvement were 0.98 and 2.96 per 100-patient-year, respectively (p = 0.02).

Among these 18 recurrences, 9 occurred in the INAH group and 9 in the non-INAH group (Figure 1). The rates of recurrence of TB in the INAH and non-INAH groups were 1.59 and 1.74 per 100 patient-years after 13.2 ± 7.7 and 10.8 ± 5.5 years of followup, respectively (p = 0.72). However, patients in the INAH group were found to have a higher rate of relapse of SLE (0.27 ± 0.26/patient-year) than those in the non-INAH group (0.18 ± 0.24/patient-year) (p = 0.07). Similarly, the INAH group received a higher cumulative dose of prednisolone per patient-year (2768.2 ± 2367.9 mg) than the non-INAH group (2265.1 ± 3019.0 mg) (p = 0.03).

Case-controlled study. In view of the higher number of flares of SLE and cumulative dose of corticosteroid used in the INAH group and a different rate of recurrence depending on the initial site of TB involvement, a 1:1 case-control analysis was performed. Patients were matched with regard to these three aspects. Table 4 shows the characteristics of these 2 groups of patients.

There were 21 patients in each group. Six patients developed TB recurrence during followup (Figure 2). Patients in the INAH group were given on average 12.4 ± 7.3 (median 11.0) months of INAH per episode of augmentation of prednisolone to ≥ 15 mg/day. The number of recurrences of TB

Table 3. Patient characteristics in INAH and non-INAH groups at baseline. Patients in the INAH group did not differ from the non-INAH group in terms of their clinical features, number of SLE flares, cumulative corticosteroid use, and previous site of TB involvement at baseline.

	INAH Treated, n = 33 No. (%)	Non-INAH Treated, n = 43 No. (%)	p
Demographics at baseline			
Female:male	30:3	40:3	1.00
Age at study, yrs	44.6 ± 9.9*	47.5 ± 12.7*	0.81
Age at onset of SLE, yrs	28.3 ± 9.7*	34.0 ± 12.5*	0.08
Duration of followup of SLE, yrs	13.4 ± 8.0*	11.3 ± 5.4*	0.25
Lupus manifestations at baseline			
Photosensitivity	9 (27.3)	11 (25.6)	1.00
Discoid rash	17 (51.5)	14 (32.6)	0.11
Oral ulceration	7 (21.2)	11 (25.6)	0.79
Malar rash	27 (81.8)	26 (60.5)	0.08
Polyarthralgia	29 (87.9)	37 (86.0)	1.00
Lupus nephritis	20 (60.6)	22 (51.2)	0.49
Serositis	11 (33.3)	20 (46.5)	0.35
Neuropsychiatric lupus	9 (27.3)	7 (16.3)	0.27
Autoimmune hemolytic anemia	27 (81.8)	27 (62.8)	0.08
Immune thrombocytopenia	20 (60.8)	21 (48.8)	0.21
Leukopenia	21 (63.6)	26 (60.5)	0.82
Site of involvement by TB at baseline			
Pulmonary	23 (53.5)	32 (66.7)	0.28
Extrapulmonary	20 (46.5)	16 (33.3)	0.28
No. of flares of SLE/patient-year at baseline	1.20 ± 1.21*	0.92 ± 1.44*	0.09
Cumulative steroid used, (mg/patient-year) at baseline	4037.0 ± 932.1*	3580.7 ± 1569.6*	0.07
Subsequent no. of patients put on INAH prophylaxis	33	—	—
Subsequent mean duration of INAH used per episode of augmentation of prednisolone to ≥ 15 mg/day, mo	15.4 ± 12.2* Median 12.0	—	—

* Results are expressed as mean ± SD.

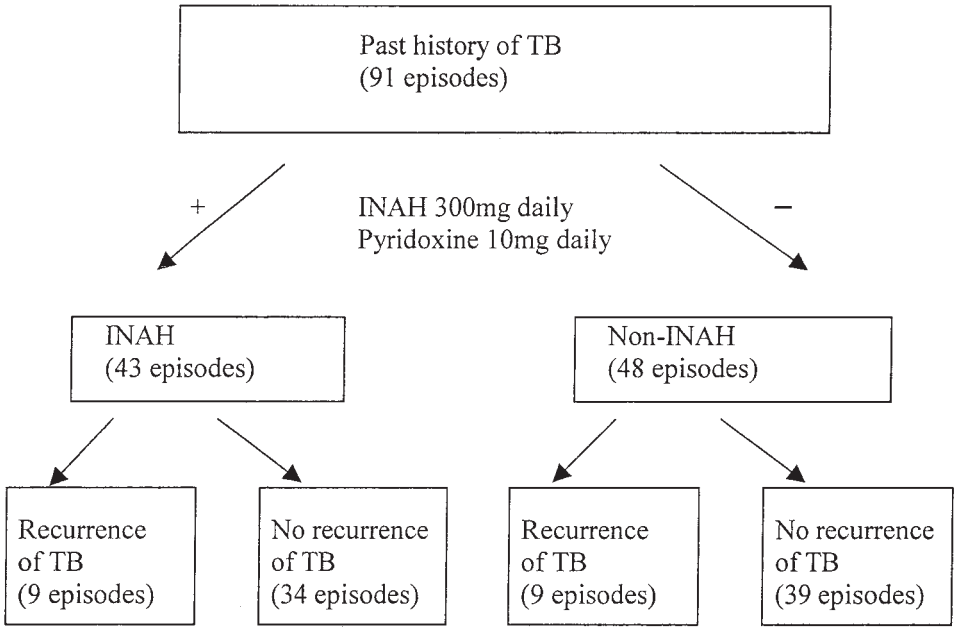

Figure 1. Recurrence of TB in 76 patients studied.

Table 4. Characteristics of patients matched for number of flares of SLE, cumulative steroid dose, and site of TB involvement. Patients in the INAH group and the non-INAH were matched for the number of flares of SLE, cumulative dose of corticosteroid used, and the initial site of TB involvement.

	INAH Treated, n = 21 No. (%)	Non-INAH Treated, n = 21 No. (%)	p
Demographics			
Female:male	18:3	20:1	0.61
Age at study, yrs	45.6 ± 10.9*	46.1 ± 9.5*	0.99
Age at onset of SLE, yrs	27.3 ± 9.3*	28.9 ± 8.3*	0.47
Age at development of TB, yrs	26.0 ± 9.9*	28.0 ± 7.8*	0.38
Duration of followup of SLE, yrs	18.3 ± 7.5*	17.2 ± 6.7*	0.45
Lupus manifestations			
Photosensitivity	7 (33.3)	9 (42.9)	0.75
Discoid rash	11 (52.4)	12 (57.1)	1.00
Oral ulceration	5 (23.8)	7 (33.3)	0.73
Malar rash	19 (90.5)	19 (90.5)	1.00
Polyarthralgia	18 (85.7)	19 (90.5)	1.00
Lupus nephritis	14 (66.7)	16 (76.2)	0.73
Serositis	5 (23.8)	5 (23.8)	1.00
Neuropsychiatric lupus	7 (33.3)	6 (28.6)	1.00
Autoimmune hemolytic anemia	16 (76.2)	18 (85.7)	0.70
Immune thrombocytopenia	13 (61.9)	14 (66.7)	1.00
Leukopenia	12 (57.1)	17 (81.0)	0.18
Site of involvement by TB			
Pulmonary	11 (52.4)	11 (52.4)	1.00
Extrapulmonary	10 (47.6)	10 (47.6)	1.00
No. of flares of SLE/patient-year	0.22 ± 0.30*	0.21 ± 0.25*	0.93
Cumulative steroid used (mg/patient-year)	1885.6 ± 1024.3*	1890.7 ± 1076.9*	0.85
Average duration of INAH used per episode of augmentation of prednisolone to ≥ 15 mg/day, mo	12.4 ± 7.3* Median 11.0	—	
No. of TB recurrences	2	4	0.66

* Results are expressed as mean ± SD.

in the INAH and non-INAH groups was 2 and 4 after 18.3 ± 7.5 and 17.2 ± 6.8 years of followup, respectively (0.55/100 patient-years and 1.04/100 patient-years; p = 0.66).

DISCUSSION

Despite the introduction of bacillus Calmette-Guerin (BCG) vaccination and effective monitoring of treatment of TB in Hong Kong in the 1950s[18], and the improvement in social hygiene and housing conditions over the years, TB remains prevalent in Hong Kong. The notification rate of TB in the year 2000-2001 was 0.11 per 100 population[20].

We found a prevalence of TB of 1.06/100 patient-years among our SLE patients, which is much higher than that of the general population. This is likely related to the intrinsic defect in cellular and humoral immune responses against infective organisms and the use of corticosteroid and immunosuppressive agents. Our reported incidence of TB in patients with SLE is substantially higher than that reported in Europe[21], but not as high as reported in India (11.6%)[22]. This difference is likely to be related to the background incidence of TB in these countries. Indeed, in other endemic areas in Southeast Asia, TB has been frequently reported in patients with SLE[23-28]. We observed a recurrence rate of 1.66/100 patient-years in SLE patients with a history of TB, hence TB remains a problem in this group of patients.

In accord with other studies on immunocompromised subjects, we found that disseminated and extrapulmonary TB are common among SLE patients. Extrapulmonary and disseminated TB were found to occur in 39.6% of TB episodes. We have also shown a different rate of recurrence of TB depending on the initial site of infection. Extrapulmonary TB was shown to have a stronger preponderance for recurrence in our patients. The risk was much higher than in those who presented initially with pulmonary TB alone (2.96 and 0.89 per 100 patient-years, respectively).

Many investigators in Western countries identify patients with latent TB infection using the purified protein derivative (PPD) test[29-31]. The use of PPD testing in this respect, however, is not a practice in our locality. First, BCG vaccination has been available in Hong Kong for over 50 years; a high false positivity rate following PPD testing is therefore expected. However, SLE patients taking corticosteroid and immunosuppressants may have impaired delayed-type hypersensitivity response and may not have a strong PPD response. A high index of clinical suspicion is therefore more important in identifying patients with latent TB infection.

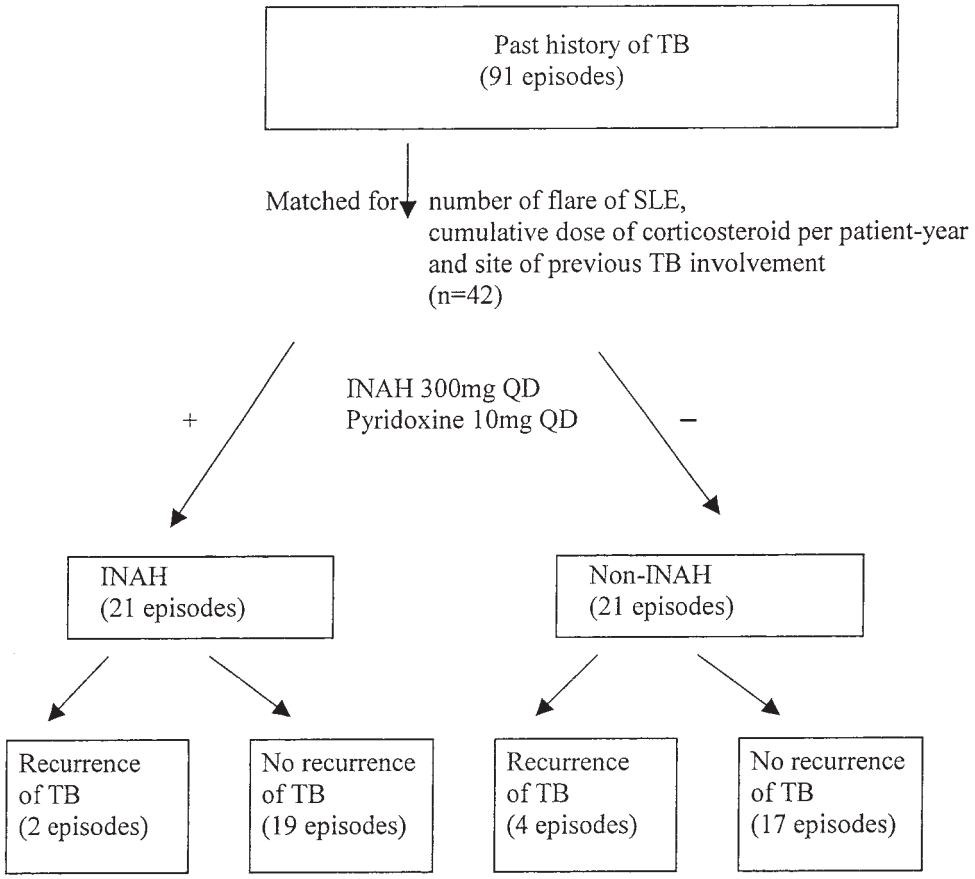

Figure 2. Recurrence of TB in a matched case-control study.

Controversies exist over the efficacy of chemoprophylaxis in patients taking corticosteroid and immunosuppressives[32-35]. In patients with other rheumatic diseases receiving immunosuppressive doses of corticosteroids, reduction in the risk of recurrence of TB has been shown to be as high as 97% with chemoprophylaxis use[36]. The only prospective but uncontrolled study on INAH prophylaxis in SLE patients[37] demonstrated a prevalence of TB of 2% compared to that of a historical control cohort of 11% of the same group surveyed years ago[22]. However, this may be related to changes in confounding factors including improvement in nutrition, sanitation and hygiene, reduction in crowded living condition, better surveillance and better drug monitoring programs, etc. Therefore, a proper prospective controlled study is required to address the efficacy of chemoprophylaxis in SLE patients. With an incidence of TB of only 1.06/100 patient-years in SLE patients, as shown in this study, a large number of patients and a long duration of followup are needed in any prospective study.

Our study examined the usefulness of INAH in SLE patients with history of TB who had previously been adequately treated. Our initial results showed that the INAH group had more flares and received higher doses of corticosteroid than the non-INAH group, and that a different level of risk of TB was indicated by the initial site of involvement of TB. We have therefore cautiously matched patients with respect to the number of flares of SLE that required immunosuppressive doses of corticosteroids, the cumulative dose of corticosteroid per patient-year, and the initial site of TB involvement. Subsequent matched case-controlled analysis of 46 matched episodes of TB with or without INAH prophylaxis revealed no difference in the rate of recurrence of TB in the 2 groups, although the recurrence rate was higher in the non-INAH group. However, a possible type II error has to be taken into account because of the small number of recurrences of TB involved (n = 6). Discordance of our results with those of previous investigators may also be related to the higher number of patients with extrapulmonary TB in our cohort.

TB remains a health risk in patients with SLE. We have demonstrated a different level of risk of recurrence of TB depending on the initial site of TB involvement. We did not find any differences in the rates of recurrence of TB in patients given INAH and those who were not, although any definite conclusions are limited by the small number of patients with TB recurrence and the retrospective design of

the study. While this was not a prospective study, we have involved a homogenous group of patients with SLE who were followed up for a prolonged period of time. Future prospective analysis should include a larger group of patients with longer duration of followup and the initial site of TB involvement taken into account.

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