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ORIGINAL RESEARCH

Knowledge and Attitudes About Screening and Preventive Treatment of Latent Tuberculosis Infection Among Patients with Rheumatic Diseases in Beijing, China

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Objective: Tuberculosis preventive treatment (TPT) is an important strategy for tuberculosis (TB) control. Rheumatic diseases (RD) patients are at high risk for active TB development. More researches are needed in terms of patient compliance in clinical practice. This study aims to explore the potential difficulties and obstacles in latent tuberculosis infection (LTBI) screening and TPT in RD patients.

Methods: Convenience sampling was used to recruit RD outpatients who had indications for LTBI screening and TPT. All participants were given questionnaires on knowledge and attitudes regarding screening and preventive treatment of LTBI.

Results: Of the 200 RD patients, most people were aware that they were at increased risk of ATB due to their rheumatic disease and knew that TB was curable. The main association with willingness to have screening for LTBI was tertiary education ($P = 0.013$). The main association with willingness to take treatment for LTBI was a sense of personal risk and belief that the treatment would reduce risk of ATB ($P < 0.001$). More than half of the people surveyed could not accept taking 6 or more pills per day, while more than half of the patients could tolerate a treatment course of 9 months or longer. Most (65.4%) preferred their own rheumatologists to initiate treatment.

Conclusion: Educating RD patients about their individual risks of TB and the side effects of treatment, and educating/empowering rheumatologists to discuss these aspects with their patients and to offer LTBI screening and treatment, may help improve patients' compliance with LTBI screening and TPT.

Keywords: rheumatic diseases, latent tuberculosis infection, tuberculosis preventive treatment, knowledge, attitudes

Introduction

Tuberculosis (TB) is the leading cause of death due to a single infectious agent. The current situation regarding TB prevention and control remains grim. Strengthening the screening and treatment of latent TB infection (LTBI) in high-risk groups is crucial for TB prevention and control efforts. Approximately 5–10% of individuals with LTBI will develop active TB during their lifetime, and tuberculosis preventive treatment (TPT) can reduce the incidence of active TB by 27%-95%.[1]

Patients with rheumatic diseases (RD) are at high risk for TB infection and active TB development due to impairment of immune function caused by the disease itself and treatment drugs. The risk of active TB is increased in patients

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receiving tumor necrosis factor-α (TNF) inhibitor therapy, and the WHO strongly recommends that patients should be screened for LTBI prior to starting TNF inhibitor treatment.[2] Additionally, the use of glucocorticoids (GCs) may also increase the risk of progression to active TB. A multicenter cross-sectional study in China showed that exposure to GCs (equivalent to prednisone) ≥30 mg/d for more than four weeks within the past two years was an independent risk factor for active TB (OR=2.031, 95% CI: 1.247–3.309).[3] Another study on RD patients with LTBI demonstrated that those receiving long-term GCs therapy (equivalent to prednisone ≥15 mg/d, treatment course for more than 4 weeks) had a significantly increased risk of developing active TB (OR: 15.64, 95% CI: 2.24–159.75).[4] Furthermore, hydroxychloroquine (RR 1.62), leflunomide (OR/RR 4.02–11.7), methotrexate (OR/RR 1.31–4.62), cyclosporine A (OR/RR 3.8–5.84), and azathioprine (OR 2.10) have been reported to increase the risk of developing active TB.[3,5] Although the WHO has not made clear recommendations on whether this population needs TPT, both the "2020 edition technical specifications for TB prevention and control in China" issued by the National Health Commission and the "Expert consensus on diagnosis and treatment of latent tuberculosis infection in patients with rheumatic diseases" recommend screening and treatment of LTBI for patients with long-term use of GCs or other immunosuppressants.

Compliance with LTBI screening and TPT among immunosuppressed populations is not optimistic. There are very limited data on the survey of compliance with LTBI screening and TPT in RD population. Some scholars have investigated the screening, initiation, and completion of TPT in human immunodeficiency virus-infected individuals, patients using biological agents, or kidney transplant recipients. The results shown that the LTBI screening rate ranged from 28% to 93.4%, with screening rates in most studies being below 70%; the initiation rate of TPT ranged from 15% to 98.7%, with initiation rates in most studies being less than 60%; among the patients who initiated TPT, completion rates ranged from 16% to 97.3%, with completion rates in most studies being below 60%.[6–17]

Whether high-risk populations can access LTBI screening and TPT depends on several factors. On one hand, patients visiting Rheumatology clinics have long relationships with individual doctors; the doctors' awareness of the TB risk and their enthusiasm for carrying out preventive treatment are important. On the other hand, it depends on patients' acceptance and compliance with LTBI screening and TPT, which often hinge on their knowledge of the disease. This study aimed to understand the knowledge and attitudes of patients with RD towards LTBI screening and TPT through a questionnaire survey, and to explore the potential difficulties and obstacles that affect the TPT process.

Materials and Methods

Study Design and Patients

This cross-sectional study was conducted in the rheumatology clinic of Peking Union Medical College Hospital using convenient sampling. The survey was carried out from April to May 2023. This study received approval from the institutional ethics committee of Peking Union Medical College Hospital (No. I-23PJ635).

Inclusion criteria were as follows: 1) age 18 years or older; 2) satisfaction of the classification criteria for RD, including systemic lupus erythematosus, Sjogren's syndrome, rheumatoid arthritis, Takayasu arteritis, Behcet's disease, dermatomyositis/polymyositis, scleroderma/systemic sclerosis, ankylosing spondylitis, psoriatic arthritis, relapsing polychondritis, overlap syndrome, undifferentiated connective tissue disease, and other systemic vasculitis; 3) use of immunosuppressive drugs (meeting at least one of the following conditions): a) current dose of glucocorticoids (equivalent to prednisone) ≥15 mg/day; b) current use of any of the following immunosuppressants: methotrexate, cyclophosphamide, cyclosporine, azathioprine, tacrolimus, mycophenolate mofetil, leflunomide, iguratimod, triptolide; c) currently using or about to use any of the following biological agents: etanercept, infliximab, adalimumab, golimumab, Benlysta, telitacicept, tofacitinib, baricitinib, upadacitinib, rituximab, secukinumab, tocilizumab. Exclusion criteria were: 1) confirmed or probable active TB; 2) receipt of anti-tuberculosis treatment in the past 2 years; 3) ongoing TPT; 4) presence of malignant tumors; 5) severe organ failure; 6) HIV infection; 7) pregnancy or lactation; 8) history of allergy to isoniazid or rifamycin.

Study Process

First, to assess patients' knowledge of active TB and LTBI, as well as their willingness to undergo TB infection screening and TPT, a preliminary questionnaire was drafted. Three experts were invited to evaluate and revise it (Supplemental Table 1).

Then, a preliminary survey was conducted among 7 patients, and split-half reliability analysis was performed using the alpha model ($\alpha = 0.717$), indicating acceptable reliability. Although the questionnaire had not undergone validity analysis, all questions were derived from existing guides on developing knowledge, attitudes, and practice surveys,[18] and previous similar questionnaires. Additionally, the questionnaire had been evaluated by three infectious diseases specialists and a psychologist experienced in sociological surveys, suggesting adequate content validity. The preliminary survey was conducted in the rheumatology clinic. Patients either self-completed the questionnaire under the researcher's supervision or had it filled out based on their responses by the researcher, ensuring comprehensive completion. Each questionnaire took approximately 5 minutes to complete, demonstrating good feasibility.

Subsequently, an interview was conducted with a rheumatologist. The interview focused on the current status of TPT, criteria for recommending TB infection screening and TPT to patients, and potential patient concerns. Based on the results from the preliminary survey and the insights gathered from the interview, the questionnaire was revised and refined. The finalized questionnaire is presented in Supplemental Table 2.

Finally, the formal questionnaires were distributed. Before respondents filled out the questionnaire, the researcher explained the survey's purpose, main content, principles of confidentiality, and voluntary participation, and obtained informed consent. The questionnaires were completed following the same procedure as the pre-survey. Throughout the process, the researcher recorded any voluntary expressions from respondents regarding their feelings about the topic and reasons for selecting specific options. Finally, all data were summarized and analyzed.

Sample Size Calculation

A convenient sample size calculation method was employed in this study, where the number of valid questionnaires required was determined as ten times the number of questions. The knowledge and attitude survey on LTBI screening and TPT comprised 20 questions. Due to some patients' inability to recall the specific sources of their TB-related knowledge, Question 20 was used solely for rough statistical purposes regarding health knowledge acquisition and was not included in correlation analyses with other variables. Thus, a total of two hundred valid questionnaires were deemed necessary for this study.

Statistical Analysis

Descriptive statistics were performed on the questionnaire responses. For categorical and ordinal variables in single-choice questions, proportions of each option chosen were calculated. For multiple-choice questions, selection rates for each option were counted. Scores and accuracy for Questions 1–4 in the active TB knowledge and attitude section were calculated using the following rules: 1 point was awarded for each correct option selected, with no points awarded if an incorrect option or no correct option was chosen. Scores across the 4 questions were totaled to form a cumulative active TB knowledge score; respondents scoring more than 5 points were considered to have better active TB knowledge. In ranking questions, when respondents showed no preference difference, each option was recorded as 1st. If only one option could be selected, it was recorded as 1st, with the other options ranked as 2nd. If only one exclusive option could be chosen, it was recorded as 3rd, with the others ranked as 1st. Categorical variables were described using frequencies and percentages. Median values and 95% confidence intervals were used to describe continuous variables. The correlation among demographic information, TB knowledge, willingness to screen for LTBI and TPT, acceptance of pill dosage and course of treatment was analyzed. Correlation between categorical variables was tested using the chi-square test, correlation between an ordinal variable and a categorical variable was tested using the rank sum test, and correlation between ordinal variables was assessed using Kendall's tau test. P values were adjusted for multiple comparisons using the Bonferroni correction. Statistical significance was considered at $P < 0.05$. All statistical analyses were performed using SPSS 26 (IBM Corp., SPSS Inc., Chicago, IL, USA) software.

Results

Demographic Characteristics

As shown in Table 1, the most prevalent disease in this study was systemic lupus erythematosus, followed by rheumatoid arthritis and ankylosing spondylitis, collectively accounting for over 70% of all respondents. The median age of the patients was 40 years, with a female-to-male ratio of approximately 3.6:1. Most patients resided in urban areas and had medical insurance. Approximately 80% of patients lived with at least one relative. More than 70% of surveyed households reported a per capita monthly income higher than the average level of Chinese urban residents. Sixty percent of the surveyed patients had a college degree or higher education. Half of the respondents were employed in enterprises, institutions, or were students, with about one-third of patients reporting an average weekly working time exceeding 8 hours (56 hours/week).

Knowledge of Active TB and LTBI

As shown in Table 2, 35% of respondents demonstrated better active TB knowledge; 55.3% believed that RD patients were more susceptible to active TB. Regarding LTBI, 75% indicated they knew "nothing", 19% claimed to know "a

Table 1 General Characteristics of 200 Patients

Variable		N	Variable		N
Age (year)	<30 (%)	40 (20.0)	Household income per capita (¥/month)	<4000 (%)	58 (29.1)
	30~39 (%)	56 (28.0)		4000~8000 (%)	63 (32.2)
	40~49 (%)	44 (22.0)		>8000 (%)	78 (39.2)
	50~64 (%)	44 (20.0)	Education level	Primary school or less (%)	12 (6.0)
	≥65 (%)	16 (8.0)		Lower secondary school (%)	31 (15.6)
Gender	Female (%)	157 (78.5)		Higher secondary school (%)	34 (17.1)
	Male (%)	43 (21.5)		University or above (%)	121 (60.8)
Residence	Urban (%)	154 (77.0)	Occupation	Employee (eg enterprises, institutions, military personnel) (%)	89 (44.5)
	Rural (%)	46 (23.0)		Unemployed (%)	15 (7.5)
Health insurance	With (%)	191 (95.5)		Retired (%)	38 (14.0)
	Without (%)	9 (4.5)		Homemakers (%)	18 (9.0)
Marital status	Divorced (%)	5 (2.5)		Students (%)	11 (5.5)
	Widowed (%)	1 (0.5)		Others (Farmers, self-employed, freelance) (%)	29 (14.5)
	Divorced (%)	5 (2.5)	Labor time (hours/day)	<4 (%)	70 (35.2)
	Widowed (%)	1 (0.5)		4~8 (%)	75 (37.7)
Type of families	Living alone (%)	37 (20.0)		8~12 (%)	64 (32.2)
	Living with partner (%)	63 (32.3)		>12 (%)	0
	Living with partner and children (%)	63 (32.3)	Type of rheumatic diseases	Systemic lupus erythematosus (%)	75 (37.5)
	Living with children only (%)	2 (1.0)		Rheumatoid arthritis (%)	48 (24.0)
	Living with parents only (%)	18 (9.2)		Ankylosing spondylitis (%)	21 (10.5)
	Living with partner and parents (%)	1 (0.5)		Takayasu arteritis (%)	8 (4.0)
	Living with partner, children and parents (%)	9 (4.6)		Sjogren syndrome (%)	7 (3.5)
	Others (%)	2 (1.0)		Others* (%)	41 (20.5)

Notes: *Other rheumatic diseases include Behcet's disease, dermatomyositis/polymyositis, systemic sclerosis/scleroderma, overlap syndrome, undifferentiated connective tissue disease, relapsing polychondritis, and eosinophilic granulomatosis with polyvessels inflammation.

Table 2 Answers to Questions Related to Knowledge of Active TB and LTBI

Question	Option	Selected Rate (%)
What do you consider to be the primary cause of tuberculosis?	Bacteria	53.5
	Heavy manual labour	11.5
	Genetics	12
What do you think are the typical symptoms of active tuberculosis?	Coughing and expectoration	80
	Hemoptysis	51
	Fever	39.5
	Weakness or emaciation	34.5
	Abdominal pain	5.5
How do you think tuberculosis can be transmitted to others?	Coughing	61
	Spitting	60.5
	Sneezing	57
	Sharing utensils	37.5
	Blood transmission	23.5
	Skin contact	4
Do you think tuberculosis is usually curable?	Yes	76.5
	No	11
	I do not know	12.5
Score of active tuberculosis knowledge	≥5 points	35
	0~4 points	65
Is there any difference in the risk of tuberculosis among people with rheumatic diseases compared with other people?	About the same	19.1
	Patients with rheumatic diseases are more likely to develop tuberculosis	55.3
	Patients with rheumatic diseases are less likely to develop tuberculosis	2.0
	I do not know	23.6
Do you know about latent tuberculosis infection?	Familiar with	6
	Know a little bit	19
	I do not know	75
Do you think latent tuberculosis infection can turn into active tuberculosis?	Yes	66.7
	No	4.2
	I cannot tell	29.2
Do you think tuberculosis preventive treatment can reduce the risk of active tuberculosis?	Yes	75.5
	No	4.1
	I cannot tell	20.4

Abbreviations: TB, tuberculosis; LTBI, latent tuberculosis infection.

little", and 6% reported being "familiar" with LTBI. Among those with some knowledge of LTBI, 66.7% (32/48) believed LTBI could progress to active TB, and 75.5% (37/49) believed TPT could mitigate the risk of active TB development.

Acceptance and Concerns About LTBI Screening and TPT

About 82% (164/200) of the respondents were willing to undergo LTBI screening as recommended by their doctors. Twenty-three respondents were unwilling to undergo LTBI screening, and 13 respondents were undecided. As shown in Figure 1A, among the 30 patients who expressed concerns, 80% (24/30) believed they were unlikely to contract TB. Approximately 76.5% (153/200) of the respondents were willing to undergo TPT as recommended by their doctors. Among the 23 patients who were unwilling or undecided about TPT, 22 provided reasons for their decision. As shown in Figure 1B, the most common reason cited was concern about drug side effects (15/22, 68.2%), followed by perceived low risk of TB contraction and difficulty with daily pill intake (both 7/22, 31.8%).

Factors Influencing the Attitudes of LTBI Screening and TPT

As shown in Table 3, the educational level of respondents willing to undergo LTBI screening was significantly higher than that of patients who declined screening ($Z = -2.484$, $P = 0.013$). Willingness to undergo LTBI screening did not significantly correlate with age, gender, residence, marital status, family type, presence of medical insurance, occupation, working hours, type of RD, knowledge level of active TB, or attitude towards TB stigma. Further analysis revealed that compared to patients uncertain about their willingness, a higher proportion of those willing to undergo screening understood the increased risk of LTBI reactivation (61.3% vs 7.7%, $P < 0.001$). As depicted in Table 4, a higher proportion of patients willing to receive TPT understood the increased risk of LTBI reactivation (61.4% vs 23.1%, $P < 0.001$) and the efficacy of TPT (83.0% vs 0, $P < 0.001$). Acceptance of TPT did not significantly correlate with age, gender, residence, marital status, family type, presence of medical insurance, income, educational level, occupation, working hours, type of RD, or knowledge level of active TB.

Preference for TPT

One hundred and sixty-three respondents who were willing to accept TPT expressed their acceptance of the pill burden and treatment duration. As shown in Figure 2A, 41.1% of patients believed they could tolerate any number of anti-tuberculosis drugs per day, while 30.7% of patients said they could not tolerate even adding just three more pills to their current regimen. More than half of the surveyed individuals could not accept taking six or more pills per day. Regarding RD patients, acceptance of TPT duration was more favorable than acceptance of pill burden. As shown in Figure 2B, approximately 42.3% of respondents indicated they could tolerate any treatment duration, and more than half of the patients could accept a treatment course of 9 months or longer. Moreover, 65.4% (106/162) of patients preferred to receive TPT from rheumatologists rather than infectious diseases physicians.

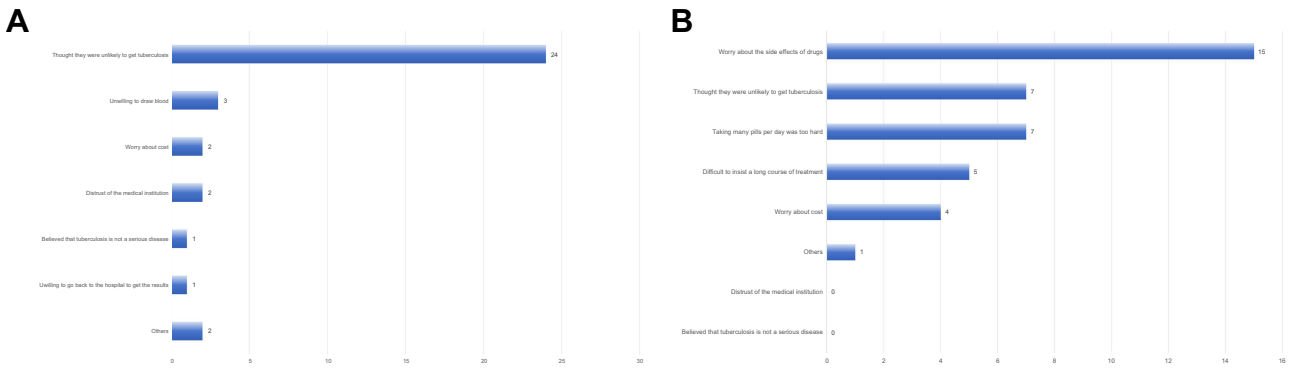

Figure 1 Reasons for refusing screening for tuberculosis infection and tuberculosis preventive treatment. (**A**) Reasons for unwillingness to undergo latent tuberculosis infection screening (person-time) (n=30). (**B**) Reasons for unwillingness to undergo tuberculosis preventive treatment (person-time) (n=22).

Table 3 Factors Influencing Acceptance of Tuberculosis Infection Screening

Variable	Acceptance of Tuberculosis Infection Screening			
	Accept (n=164)	Refuse (n=23)	Z/X^2	*P*
Age (year)				
<30 (%)	20.7	17.4	1.490	0.828
30~39 (%)	28.7	21.7		
40~49 (%)	22.0	21.7		
50~64 (%)	21.3	26.1		
≥65 (%)	7.3	13.0		
Female (%)	78.0	87.0	0.970	0.325
Living in urban (%)	79.3	65.2	2.287	0.130
Having health insurance (%)	95.7	95.7	0.000	0.986
Marital status				
Unmarried (%)	26.2	13.0	1.924	0.382
Married (%)	70.7	82.6		
Divorced and widowed (%)	3.0	0.0		
Types of families				
Living alone (%)	18.1	13.0	3.808	0.283
Living with partner (%)	31.3	43.5		
Living with partner and children (%)	32.5	39.1		
Others (%)	18.1	4.3		
Household income per capita (¥/month)				
<4000 (%)	26.4	34.8	−0.794	0.427
4000~8000 (%)	32.5	30.4		
>8000 (%)	41.1	34.8		
Education level				
Primary school or less (%)	5.5	8.7	−2.484	0.013
Lower secondary school (%)	15.3	21.7		
Higher secondary school (%)	13.5	34.8		
Tertiary education (%)	65.6	34.8		
Occupation				
Employee (enterprises, institutions, military personnel) (%)	46.3	34.8	4.051	0.256
Retired (%)	17.7	30.4		
Students (%)	6.7	0		
Unemployed, homemakers and others (%)	29.3	34.8		
Labor time (hours/day)				
<4 (%)	33.1	52.2	−1.198	0.231
4~8 (%)	39.9	21.7		
8~12 (%)	27.0	26.1		
Rheumatic diseases				
Systemic lupus erythematosus (%)	38.4	39.1	0.279	0.964
Rheumatoid arthritis (%)	25.0	21.7		
Ankylosing spondylitis (%)	10.4	8.7		
Others (%)	26.2	30.4		
The risk of active TB in rheumatic diseases patients				
About the same (%)	16.0	21.7	4.423	0.219
Patients with rheumatic immune diseases are more likely to develop tuberculosis (%)	61.3	39.1		
Patients with rheumatic immune diseases are less likely to develop tuberculosis (%)	1.8	4.3		
I do not know (%)	20.9	34.8		
Score of active TB knowledge (points, median, IQR)	4.0 (4.0–4.0)	4.0 (2.0–4.0)	−1.694	0.090
Better active TB knowledge (%)	37.8	21.7	2.264	0.132
Knowledge about LTBI				
Familiar with (%)	7.3	0	2.320	0.313
Know a little bit (%)	18.3	26.1		
I do not know (%)	74.4	73.9		
Whether LTBI can turn into active TB				
Yes (%)	72.5	50.0	1.248	0.264
No or cannot tell (%)	27.5	50.0		

(*Continued*)

Table 3 (Continued).

Variable	Acceptance of Tuberculosis Infection Screening			
	Accept (n=164)	Refuse (n=23)	Z/X^2	*P*
Whether be discriminated if you have active TB?				
Yes (%)	34.1	39.1	0.240	0.887
No (%)	50.6	47.8		
I cannot tell (%)	15.2	13.0		

Abbreviations: TB, tuberculosis; LTBI, latent tuberculosis infection.

Table 4 Factors Influencing Acceptance of Tuberculosis Preventive Treatment

Variable	Acceptance of Tuberculosis Preventive Treatment			
	Accept (n=153)	Refuse (n=13)	Z/X^2	*P*
Age (year)				
<30 (%)	20.9	7.7	5.149	0.272
30~39 (%)	30.7	15.4		
40~49 (%)	21.6	23.1		
50~64 (%)	20.3	38.5		
≥65 (%)	6.5	15.4		
Female (%)	77.8	76.9	0.005	0.934
Living in urban (%)	79.7	61.5	2.337	0.126
Having health insurance (%)	94.8	100.0	0.714	0.398
Marital status				
Unmarried (%)	26.1	23.1	0.437	0.804
Married (%)	71.2	76.9		
Divorced and widowed (%)	2.6	0.0		
Types of families				
Living alone (%)	20.1	15.4	0.285	0.963
Living with partner (%)	32.2	38.5		
Living with partner and children (%)	31.5	30.8		
Others (%)	16.1	15.4		
Household income per capita (¥/month)				
<4000 (%)	27.0	38.5	−0.899	0.369
4000~8000 (%)	32.2	30.8		
>8000 (%)	40.8	30.8		
Education level				
Primary school or less (%)	5.9	0.0	−1.229	0.219
Lower secondary school (%)	15.3	21.7		
Higher secondary school (%)	13.5	34.8		
Tertiary education (%)	65.6	34.8		
Occupation				
Employee (enterprises, institutions, military personnel) (%)	46.4	38.5	0.540	0.910
Retired (%)	17.6	15.4		
Students (%)	5.9	7.7		
Unemployed, homemakers and others (%)	30.1	38.5		
Labor time (hours/day)				
<4 (%)	31.6	38.5	−0.852	0.394
4~8 (%)	40.8	46.2		
8~12 (%)	27.6	15.4		
Rheumatic diseases				
Systemic lupus erythematosus (%)	39.2	23.1	5.829	0.120
Rheumatoid arthritis (%)	24.2	23.1		
Ankylosing spondylitis (%)	11.8	0.0		
Others (%)	24.8	53.8		

(*Continued*)

Table 4 (Continued).

Variable	Acceptance of Tuberculosis Preventive Treatment			
	Accept (n=153)	Refuse (n=13)	Z/X^2	*P*
The risk of active TB in rheumatic diseases patients				
About the same (%)	16.3	38.5	20.476	<0.001
Patients with rheumatic immune diseases are more likely to develop tuberculosis (%)	61.4	23.1		
Patients with rheumatic immune diseases are less likely to develop tuberculosis (%)	0.7	15.4		
I do not know (%)	21.6	23.1		
Score of active TB knowledge (points, median, IQR)	4.0 (4.0–4.0)	4.0 (2.0–6.0)	−0.272	0.785
Better active TB knowledge (%)	34.0	38.5	0.106	0.744
Whether be embarrassed when taking anti-TB drugs in public				
Yes (%)	33.3	38.5	0.141	0.932
No (%)	58.2	53.8		
I cannot tell (%)	8.5	7.7		
Knowledge about LTBI				
Familiar with (%)	5.9	7.7	1.047	0.592
Know a little bit (%)	19	7.7		
I do not know (%)	75.2	84.6		
Whether LTBI can turn into active TB				
Yes (%)	66.7	50.0	0.234	0.629
No or cannot tell (%)	33.3	50.0		
Whether TPT can reduce the risk of developing active TB				
Yes (%)	83.8	0	8.169	0.004
No or cannot tell (%)	16.2	100		

Abbreviations: TB, tuberculosis; LTBI, latent tuberculosis infection.

Discussion

The entire process of LTBI screening and TPT involves screening the target population for TB infection, excluding active TB, initiating TPT, and ensuring adherence to the full course of medication. Challenges at any of these stages may result in patient dropout.

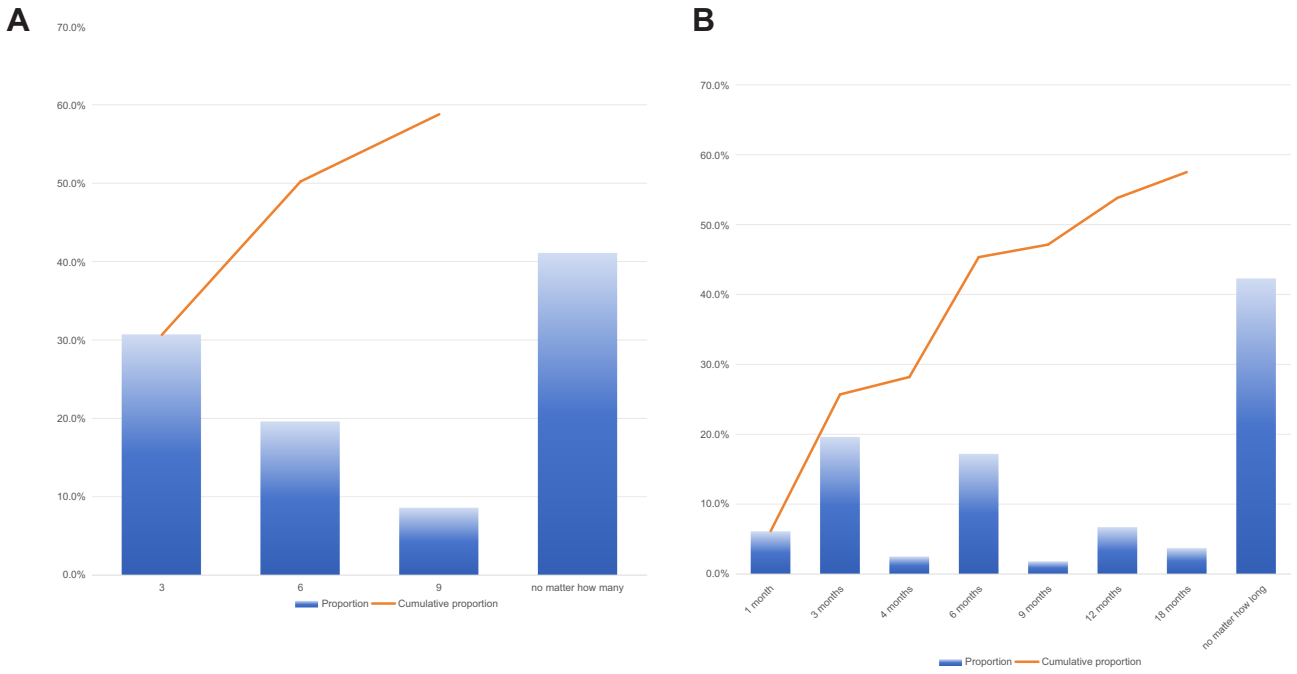

Figure 2 Preference for tuberculosis preventive treatment. (**A**) Minimum number of anti-tuberculosis pills that cannot be tolerated. (**B**) Maximum duration of treatment that can be tolerated.

In this study, 82% of the respondents were willing to undergo LTBI screening as recommended by their doctors, whereas two studies from Japan reported screening rates for patients treated with TNF inhibitor ranging from 40% to 66%.[16,19] The potential reason for this variance may lie in doctors not consistently recommending screening for high-risk populations. Furthermore, the questionnaire survey results solely reflect patients' willingness to undergo LTBI screening, and the actual LTBI screening rate requires further investigation. This study found that the level of education was associated with screening willingness. There was no significant difference in active TB knowledge between patients who clearly expressed willingness to undergo screening and those who were unwilling. However, compared with patients uncertain about screening willingness, a higher proportion of those willing to undergo screening believed that RD patients face a higher risk of developing active TB than the general population. This suggests that enhancing patients' understanding of LTBI reactivation risk could help alleviate uncertainties about LTBI screening among those with ambiguous attitudes. Among patients unwilling to undergo screening, 80% believed they were unlikely to contract TB, underscoring insufficient awareness of the risk of active TB development among RD patients as a primary barrier to LTBI screening.

In this study, 76.5% of the respondents were willing to undergo TPT as recommended by their doctors. However, some individuals may ultimately decline treatment in clinical practice upon learning about side effects, costs, pill burden, and treatment duration. Yuan et al, in a study on college students with LTBI in Shandong province, reported that among those initially willing to accept TPT, 60.3% eventually refused it; medical students and students with higher knowledge levels about TB were less likely to refuse TPT.[20] Additionally, previous studies have demonstrated that discussing TPT with healthcare providers and possessing a higher understanding of TB and the risk of developing active TB are associated with greater acceptance of TPT.[20,21] Similarly, our study found that patients who perceive a higher risk of developing active TB in the RD population and recognize the benefits of TPT are more likely to accept it. These findings indicate that patient education could potentially enhance TPT acceptance.

Concerns about the adverse effects of drugs are a common reason for refusing TPT. Previous studies on healthcare workers have also indicated that individuals who express concerns about drug side effects, have underlying liver disease, or are taking hepatotoxic drugs are less likely to initiate TPT.[21,22] These results indicate that concerns about adverse drug reactions persist regardless of patients' medical knowledge. For patients with RD, the interaction between RD medications and anti-TB drugs introduces additional apprehension. During our study, some respondents clearly expressed the need for physicians to consider these drug interactions. Demonstrating to patients that the recommendation for drug prophylaxis is made after fully considering treatment benefits and the risks of adverse reactions, and providing detailed explanations on monitoring and managing adverse reactions, may help alleviate concerns among RD patients regarding the adverse effects of anti-TB drugs.

Several studies have shown that compared with isoniazid alone for six or nine months, short-term regimens such as rifampicin alone for four months, or isoniazid and rifamycin for three months, can achieve higher completion rates for TPT.[23–29] However, our study found that nearly half of the patients could tolerate a treatment course of nine months or longer. In terms of treatment duration, all currently recommended regimens are acceptable for most patients. This may be because RD patients have experience in managing diseases that require long-term treatment and management. On the other hand, more than half of the patients could not tolerate an increase in the daily number of anti-TB drugs to six tablets. This may be attributed to the fact that patients with RD often already require multiple medications to treat their primary disease, leaving less tolerance for additional pills. Therefore, compared with shortening the treatment course, the use of combination preparations may be more meaningful in reducing pill burden and improving TPT compliance among RD patients.

Previous surveys and interviews among TB contacts and health service providers indicate that TPT regimens involving smaller and fewer pills, shorter treatment durations, reduced frequency of doctor visits, shorter waiting times for follow-up visits, and lower costs are more popular. Research on people living with human immunodeficiency virus (PLHIV) suggests that integrating TPT into routine processes and disseminating TPT knowledge among PLHIV can improve tuberculosis infection screening rates, TPT initiation rates, and completion rates.[9,13] This experience can be extended to RD patients, who typically receive long-term care from the same rheumatologist, fostering a close and trusting patient-doctor relationship. Conducting TPT in rheumatology clinics can save

patients time and reduce economic costs associated with registering at multiple departments, waiting times, visits, and travel to and from the hospital. Moreover, physicians' familiarity with the patients' conditions can help alleviate patient concerns about screening and TPT. The results of this study support this notion: most patients prefer to undergo TPT in rheumatology clinics rather than being referred to infectious disease departments or seeking medical services independently. Several patients cited their preference based on wanting physicians to consider their overall health situation as RD patients. Based on this, we propose that the concerns about treatment duration and side effects could be addressed by education and empowerment of both patients and rheumatologists.

This study is the first investigation into the knowledge and attitudes of patients with RD towards LTBI screening and TPT. It reveals potential difficulties and obstacles in the LTBI screening and TPT process and holds significant implications for improving adherence in clinical practice. However, this study has some limitations. Firstly, the questionnaire only assessed RD patients' willingness to undergo LTBI screening and TPT, which may differ from actual acceptance rates in clinical decision-making. Secondly, the study did not collect information on factors such as the duration of RD, current medications, economic and time costs associated with treating the primary disease, or history of adverse drug reactions. These factors could potentially impact patient compliance. Further studies addressing these aspects are warranted.

Conclusion

In summary, educating RD patients about their individual risks of TB and the side effects of treatment, and educating/empowering rheumatologists to discuss these aspects with their patients and to offer LTBI screening and treatment, may help improve patients′ compliance with LTBI screening and TPT.

Ethical Approval

The studies involving human participants were reviewed and approved by the Ethics Committee of PUMCH (No: I-23PJ635). The study was conducted in accordance with the Helsinki principles.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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References

1. Mølhave M, Wejse C. Historical review of studies on the effect of treating latent tuberculosis. *Int J Infect Dis*. 2020;92S:S31–S36. doi:10.1016/j.ijid.2020.03.011
2. World Health organization. WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment: module 1: prevention. World Health Organization; 2020. Available from: https://www.who.int/publications/i/item/9789240001503. Accessed August 2, 2024.
3. Liu X, Zhang L, Zhang F, et al. Prevalence and risk factors of active tuberculosis in patients with rheumatic diseases: a multi-center, cross-sectional study in China. *Emerg Microbes Infect*. 2021;10(1):2303–2312. doi:10.1080/22221751.2021.2004864
4. Long W, Cai F, Wang X, et al. High risk of activation of latent tuberculosis infection in rheumatic disease patients. *Infect Dis*. 2020;52(2):80–86. doi:10.1080/23744235.2019.1682187
5. Cantini F, Niccoli L, Capone A, et al. Risk of tuberculosis reactivation associated with traditional disease modifying anti-rheumatic drugs and non-anti-tumor necrosis factor biologics in patients with rheumatic disorders and suggestion for clinical practice. *Expert Opin Drug Saf*. 2019;18(5):415–425. doi:10.1080/14740338.2019.1612872
6. Adams JW, Howe CJ, Andrews AC, et al. Tuberculosis screening among HIV-infected patients: tuberculin skin test vs. interferon-gamma release assay. *AIDS Care*. 2017;29(12):1504–1509. doi:10.1080/09540121.2017.1325438

7. Chandra DK, Moll AP, Altice FL, et al. Structural barriers to implementing recommended tuberculosis preventive treatment in primary care clinics in rural South Africa. *Glob Public Health*. 2022;17(4):555–568. doi:10.1080/17441692.2021.1892793
8. Roscoe C, Lockhart C, de Klerk M, et al. Evaluation of the uptake of tuberculosis preventative therapy for people living with HIV in Namibia: a multiple methods analysis. *BMC Public Health*. 2020;20(1):1838. doi:10.1186/s12889-020-09902-z
9. Page-Shipp L, Lewis JJ, Velen K, et al. Household point of care CD4 testing and isoniazid preventive therapy initiation in a household TB contact tracing programme in two districts of South Africa. *PLoS One*. 2018;13(3):e0192089. doi:10.1371/journal.pone.0192089
10. Goletti D, Navarra A, Petruccioli E, et al. Latent tuberculosis infection screening in persons newly-diagnosed with HIV infection in Italy: a multicentre study promoted by the Italian Society of Infectious and Tropical Diseases. *Int J Infect Dis*. 2020;92:62–68. doi:10.1016/j.ijid.2019.12.031
11. Melgar M, Shiraishi RW, Tende C, et al. Assessment of the tuberculosis case-finding and prevention cascade among people living with HIV in Zambia - 2018: a cross-sectional cluster survey. *BMC Public Health*. 2021;21(1):859. doi:10.1186/s12889-021-10929-z
12. Kalema N, Semeere A, Banturaki G, et al. Gaps in TB preventive therapy for persons initiating antiretroviral therapy in Uganda: an explanatory sequential cascade analysis. *Int J Tuberc Lung Dis*. 2021;25(5):388–394. doi:10.5588/ijtld.20.0956
13. Lwevola P, Izudi J, Kimuli D, et al. Low level of tuberculosis preventive therapy incompletion among people living with Human Immunodeficiency Virus in eastern Uganda: a retrospective data review. *J Clin Tuberc Other Mycobact Dis*. 2021;25:100269. doi:10.1016/j.jctube.2021.100269
14. Thindwa D, MacPherson P, Choko AT, et al. Completion of isoniazid preventive therapy among human immunodeficiency virus positive adults in urban Malawi. *Int J Tuberc Lung Dis*. 2018;22(3):273–279. doi:10.5588/ijtld.17.0370
15. Shapiro AE, van Heerden A, Schaafsma TT, et al. Completion of the tuberculosis care cascade in a community-based HIV linkage-to-care study in South Africa and Uganda. *J Int AIDS Soc*. 2018;21(1):e25065. doi:10.1002/jia2.25065
16. Tomio J, Yamana H, Matsui H, et al. Tuberculosis screening prior to anti-tumor necrosis factor therapy among patients with immune-mediated inflammatory diseases in Japan: a longitudinal study using a large-scale health insurance claims database. *Int J Rheum Dis*. 2017;20(11):1674–1683. doi:10.1111/1756-185X.13190
17. Simkins J, Abbo LM, Camargo JF, et al. Twelve-week rifapentine plus isoniazid versus 9-month isoniazid for the treatment of latent tuberculosis in renal transplant candidates. *Transplantation*. 2017;101(6):1468–1472. doi:10.1097/TP.0000000000001329
18. World Health organization. Advocacy, communication and social mobilization for TB control: a guide to developing knowledge, attitude and practice surveys. World Health Organization; 2008. Available from: https://www.who.int/publications/i/item/9789241596176. Accessed August 2, 2024.
19. Iba A, Tomio J, Yamana H, et al. Tuberculosis screening and management of latent tuberculosis infection prior to biologic treatment in patients with immune-mediated inflammatory diseases: a longitudinal population-based analysis using claims data. *Health Sci Rep*. 2020;3(4):e216. doi:10.1002/hsr2.216
20. Yuan Y, Jin J, Bi X, et al. Factors associated with refusal of preventive therapy after initial willingness to accept treatment among college students with latent tuberculosis infection in Shandong, China. *BMC Infect Dis*. 2023;23(1):38. doi:10.1186/s12879-023-08005-5
21. Bar-Meir M, Pariente G, Romem A, et al. Identifying factors affecting latent tuberculosis treatment acceptance among healthcare workers: a retrospective analysis in a tertiary care centre. *BMJ Open*. 2021;11(9):e047444. doi:10.1136/bmjopen-2020-047444
22. Lee EH, Kim SJ, Ha EJ, et al. Treatment of latent tuberculous infection among health care workers at a tertiary hospital in Korea. *Int J Tuberc Lung Dis*. 2018;22(11):1336–1343. doi:10.5588/ijtld.18.0280
23. Sentís A, Vasconcelos P, Machado RS, et al. Failure to complete treatment for latent tuberculosis infection in Portugal, 2013–2017: geographic-, sociodemographic-, and medical-associated factors. *Eur J Clin Microbiol Infect Dis*. 2020;39(4):647–656. doi:10.1007/s10096-019-03765-y
24. Swift MD, Molella RG, Vaughn AIS, et al. Determinants of latent tuberculosis treatment acceptance and completion in healthcare personnel. *Clin Infect Dis*. 2020;71(2):284–290. doi:10.1093/cid/ciz817
25. Eastment MC, McClintock AH, McKinney CM, et al. Factors that influence treatment completion for latent tuberculosis infection. *J Am Board Fam Med*. 2017;30(4):520–527. doi:10.3122/jabfm.2017.04.170070
26. Moro RN, Borisov AS, Saukkonen J, et al. Factors associated with noncompletion of latent tuberculosis infection treatment: experience from the PREVENT TB Trial in the United States and Canada. *Clin Infect Dis*. 2016;62(11):1390–1400. doi:10.1093/cid/ciw126
27. Ronald LA, FitzGerald JM, Bartlett-Esquilant G, et al. Treatment with isoniazid or rifampin for latent tuberculosis infection: population-based study of hepatotoxicity, completion and costs. *Eur Respir J*. 2020;55(3):1902048. doi:10.1183/13993003.02048-2019
28. Arguello Perez E, Seo SK, Schneider WJ, et al. Management of latent tuberculosis infection among healthcare workers: 10-year experience at a single center. *Clin Infect Dis*. 2017;65(12):2105–2111. doi:10.1093/cid/cix725
29. Kim BK, Kim HJ, Kim HJ, et al. Experiences of latent tuberculosis infection treatment for the North Korean refugees. *Tuberc Respir Dis*. 2019;82(4):306–310. doi:10.4046/trd.2019.0034