# Risk of latent tuberculosis in the cohort of patients with rheumatoid arthritis in Slovakia

**Malinová J.[1], Hájková M.[2], Hatalová A.[3], Šteňová E.[1]**

[1]1st Department of Internal Medicine, Faculty of Medicine, Comenius University in Bratislava and University Hospital Bratislava, Slovakia
[2]Department of Pneumology and Phthiseology, Faculty of Medicine, Comenius University in Bratislava and University Hospital Bratislava, Slovakia
[3]Department of Hematology and Transfusiology, Faculty of Medicine, Comenius University in Bratislava and University Hospital Bratislava, Slovakia

## ABSTRACT

**Aim:** This study aims to determine the prevalence of latent tuberculosis infection (LTBI) in patients with moderate to severe rheumatoid arthritis (RA) who receive conventional and anti-cytokine therapy, to identify possible risk factors for tuberculosis (TB) and to evaluate the prophylactic treatment in positively screened patients.

**Patient and Methods**: We conducted an observational, retrospective study in patients with RA, who underwent LTBI screening (chest X-ray, tuberculin skin test and interferon gamma release assay test – IGRA test).

**Results**: Out of 124 patients included, 7.25% of patients were diagnosed with LTBI during the treatment with conventional synthetic anti-rheumatic drugs in combination with glucocorticoids before initiation of anti-cytokine therapy. Another 21.77% were diagnosed during treatment with biologics or Janus kinase inhibitors. We confirmed the highest incidence of LTBI in TNF-treated group (66.66% LTBI positive patients), but also found positive screening in patients treated with other modalities. The mean LTBI detection time since the initiation of anti-cytokine therapy was 39.5 months (12–134 months). Active TB with clinical manifestation has occurred in one patient. Statistical analysis did not show an association between risk of LTBI and age, sex or treatment modality.

**Conclusion**: The results of this study confirm the necessity of LTBI screening and long-term monitoring in RA patients treated with any kind of anti-cytokine therapy. The currently used national recommendations are sufficiently sensitive to identify TB in these patients. There remains a question of screening and prophylactic antituberculosis therapy in patients treated with conventional synthetic anti-rheumatic drugs in combination with glucocorticoids.

**KEYWORDS**

IGRA test – mycobacterial infection – biological treatment – latent tuberculosis infection

## SÚHRN

**Malinová J., Hájková M., Hatalová A., Šteňová E.: Riziko latentnej tuberkulózy u pacientov s reumatoidnou artritídou na Slovensku**

**Ciele práce:** Cieľom práce bolo zistiť prevalenciu latentnej tuberkulózy (LTBI) u pacientov s reumatoidnou artritídou stredne ťažkého a ťažkého stupňa liečených konvenčnou a anticytokínovou terapiou, identifikovať možné rizikové faktory tuberkulózy (TB) a hodnotiť efektivitu profylaktickej liečby u pozitívne skrínovaných pacientov.

**Pacienti a metodika:** Observačná retrospektívna štúdia so zaradením pacientov s reumatoidnou artritídou po absolvovaní skríningových vyšetrení na zistenie LTBI (röntgenologické vyšetrenie hrudníka, tuberkulínový kožný test, interferon gamma release assay test – IGRA test).

**Výsledky:** V skupine 124 pacientov sme zistili u 7,25 % LTBI počas kombinovanej liečby konvenčným syntetickým liečbu modifikujúcim antireumatikom (csDMARD) a kortikoterapiou. U ďalších 21,77 % LTBI bola diagnostikovaná počas biologickej liečby alebo terapie inhibítorom Janusových kináz. Najvyššia incidencia LTBI bola zistená v skupine pacientov liečených inhibítormi tumor nekrotizujúceho faktoru (66,66 % z LTBI pozitívnych pacientov), avšak pozitívne skrínovaní pacienti sa vyskytli aj pri liečbe inými modalitami. Priemerná doba detekcie LTBI pozitivity bola 39,5 mesiacov (12–134 mesiacov) od začatia anticytokínovej terapie. Klinicky manifestná aktívna TB sa potvrdila u jedného pacienta. Štatistická analýza nepreukázala asociáciu medzi rizikom LTBI a vekom, pohlavím alebo liečebnou modalitou.

**Záver:** Výsledky tejto štúdie potvrdzujú opodstatnenie skríningu a stáleho monitorovania LTBI u pacientov s RA liečených anticytokínovou terapiou. Naše aktuálne národné odporúčania sú dostatočne senzitívne na identifikáciu LTBI. Nezodpovedanou otázkou zostáva potreba skríningu a profylaktickej liečby antituberkulotikami u pacientov liečených csDMARD v kombinácii s glukokortikoidmi.

**KĽÚČOVÉ SLOVÁ**

IGRA test – infekcia mykobaktériami – biologická liečba – latentná tuberkulózna infekcia

*Epidemiol Mikrobiol Imunol, 2021;70(2):83–90*

## INTRODUCTION

Tuberculosis (TB) is one of the deadliest and most feared infectious diseases in the 21st century. At least 10 million people get TB, and more than 1.5 million people die from it each year [1]. A new infection occurs in about 10 million people and another 2 to 3 billion of the world's population is estimated to be infected with *Mycobacterium tuberculosis* (MT) without clinical signs of TB [1]. Latent tuberculosis infection (LTBI) is characterized by the presence of immune responses to MT infection without clinical evidence of active TB. Approximately in 5–10% of people, LTBI infection will progress to active TB during their lifetime. Slovakia is a country with a low incidence of TB. In 2017, 249 patients were diagnosed with TB (prevalence of 4.6/100 000 population), number of new cases and relapses was 228 [2]. In most cases, the reactivation of LTBI is responsible for development of clinically symptomatic disease; therefore, it is vital to identify those with LTBI to prevent TB spreading [3].

Rheumatoid arthritis (RA) is one of the most common chronic autoimmune diseases in Europe with a prevalence of 0.8–1.1%, associated with an increased risk of TB [4, 5]. It mainly affects synovial joints, but most individuals with this condition experience also extra-articular manifestation. Some cohort and retrospective studies show a higher prevalence of LTBI in RA patients compared to the general population, and even 4-times higher incidence of TB was found. The affected immune system, higher frequency of comorbidities, and immunosuppressive treatment of RA patients put them at a higher risk of TB [4, 6].

The goal of RA therapy is to achieve remission or low disease activity. Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs, e.g. methotrexate, leflunomide and sulfasalazine) are often combined with glucocorticoids. Treatment with biological DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) is indicated in case of inadequate response to csDMARD with sustained high disease activity or if csDMARDs are contraindicated (comorbidities, adverse events). Treatment with bDMARDs and tsDMARDs, especially TNF-α (tumour necrosis factor-α) inhibitors (TNFi, e.g. infliximab, adalimumab, golimumab, certolizumab and etanercept) is associated with a high risk of TB [4]. TNF-α plays a crucial role in immune defence against MT infection by stimulating MT phagocytosis and activating formation and long-term stabilisation of granulomas. According to clinical research, there is a higher risk of LTBI in patients also treated with other biologics and therefore, this therapy requires previous LTBI screening. The screening procedure in Slovakia is determined by the Methodological Recommendation of the Chief Expert of the Ministry of Health of Slovak Republic [7].

The WHO guidelines on LTBI consider the probability of progression to active TB disease in a specific risk group. However, the management should be explicitly tailored in each country based on TB burden and resource availability [2, 3]. This study aims to determine the prevalence of LTBI in patients with moderate to severe RA treated with csDMARDs, bDMARDs/tsDMARDs, to identify possible risk factors for MT infection, and to evaluate prophylactic LTBI treatment in this group of patients.

As the prevalence and incidence of LTBI were higher than in the general population, it is crucial to identify and start prophylactic therapy in this subgroup according to local Slovak guidelines. Results from our cohort show that early intervention can prevent the development of the latent disease and its conversion into symptomatic TB with potential impact on patient's survival and morbidity. This pilot project in Slovakia opens the question of whether LTBI screening should include other severely immunocompromised patients, e.g. patients with malignancies, where the risk of LTBI is also higher. Defining the risk in those subgroups can be a subject of further clinical projects or studies.

## PATIENT AND METHODS

### Patient

The medical records of RA patients treated in the Rheumatology Clinic of University Hospital in Bratislava between 2014 and 2019 were retrospectively analyzed. We included 124 patients with moderate to severe RA fulfilling the 2010 ACR/EULAR (American College of Rheumatology/European League Against Rheumatism) classification criteria for RA. The patients underwent a comprehensive examination including a detailed medical history (with epidemiological status and vaccination), physical examination, laboratory tests of renal and liver function, acute phase reactants (erythrocyte sedimentation rate, ESR, C-reactive protein, CRP), and complete blood count. The composite index DAS28-ESR (disease activity score using 28 joint counts calculated with ESR) was used to assess disease activity (high activity was defined as DAS28 > 5.1), and functional status was evaluated based on HAQ (Health Assessment Questionnaire). Radiological stage of disease was evaluated according to X-ray Steinbrocker´s classification. Therapy with bDMARD/tsDMARD was started if the patient did not achieve a treatment target with csDMARDs and still had a high disease activity.

The patients´ records provided information included demographic data, clinical characteristics of the disease, and serological markers (RF – rheumatoid factor, ACPA – anti-citrullinated protein antibody). Previous treatment was analysed over the entire duration of RA.

### LTBI screening

Prior to bDMARD/tsDMARD treatment, patients underwent a complete pneumological examination – clinical examination, Mantoux tuberculin skin test (TST), chest X-ray and IGRA test. The interpretation of TST after 72h of injection was realized by pneumologists as recommended by national guidelines: induration 0-5mm is considered as negative, diameter 6–15 mm positive, and greater than 16 mm is a hyperreactive result [7]. Patient´s blood samples were tested for LTBI using IGRA test QuantiFERON-TB Gold In-tube (QFT-GIT) in the diagnostics laboratory. A positive result suggested MT infection, while a negative result suggested an unlikely infection. Patients with positive IGRA test underwent a pneumological examination every three months in the first year and IGRA test after 12 months. In the case of IGRA positivity without clinical manifestation of TB, the patient was diagnosed with LTBI, and a course of prophylaxis was indicated according to the recommendation of MH SR guidelines [7].

The subjects provided their written informed consent for voluntary participation in the study by signing the inform consent form.

### Statistical analysis

Statistical analysis was performed using ANOVA to compare continuous variables for different factor levels of the selected variables. The Chi-square test and Fisher's test were used for binary variables. Logistic regression models were made with LTBI as a dependent variable to identify associated risk factors.

## RESULTS

We included 124 Caucasian RA patients in the study: 81.45% women and 18.55% men aged 23 through 79 years. The mean duration of disease was 12.31 ± 8.09 years. The preventive vaccination rate in the group was 100% according to the national immunization schedule created in 1953 instituted mandatory vaccination (in 2012 obligatory BCG vaccination was stopped in view of the low TB incicence). No patient has a history of active TB or LTBI, and there was one case of pulmonary TB in the family of an LTBI positive participant. Considering the occurrence of LTBI, the examination of risk factors also included the patient's smoking history. There were 19 (15.32%) active smokers.

Most patients had seropositive RA with RF (82.50%) or/and ACPA (78.22%) positivity. The mean DAS28 value of 6.03 ± 0.88, indicating high disease activity. HAQ results of our patients (1.60 ± 0.69) are indicative of a moderate functional disability. Demographic data and clinical characteristics are summarized in Table 1. There were no significant differences in reported parameters between LTBI patients and patients without LTBI evidence.

We have retrospectively evaluated csDMARD (conventional synthetic disease modifying antirheumatic drug) treatment of RA. The most commonly used drugs were methotrexate (MTX), hydroxychloroquine, and sulfasalazine either as monotherapy or in combination. Before starting bDMARD/tsDMARD (biological DMARD, target synthetic DMARD) treatment, most patients (60.48%) received methotrexate. Ten patients (8.06%)

**Table 1.** Demographic data and clinical characteristics of patients

| | | Total (n = 124) | LTBI+ve (n = 27) | LTBI-ve (n = 97) |
|---|---|---|---|---|
| **Sex female, % (n)** | | 81.45 (101) | 88.89 (24) | 79.38 (77) |
| **Age, y, mean (± SD)** | | 53.18 ± 12.46 | 54.56 ± 10.97 | 52.79 ± 12.87 |
| **Smoking history, % (n) pack years, mean (± SD)** | | 15.32 (19)<br>12.94 ± 9.8 | 11.11 (3)<br>17.5 ± 6.61 | 16.49 (16)<br>12.09 ± 10.20 |
| **BMI, kg/m², mean (± SD)** | | 25.54 ± 5.36 | 25.37 ± 4.89 | 25.59 ± 5.50 |
| **RF +ve, % (n)** | | 82.50 (99) | 81.48 (22) | 82.80 (77) |
| **ACPA+ve, % (n)** | | 78.22 (97) | 85.18 (23) | 76.28 (74) |
| **DAS28, mean (± SD)** | | 6.03 ± 0.88 | 5.95 ± 0.87 | 6.05 ± 0.89 |
| **HAQ, mean (± SD)** | | 1.60 ± 0.69 | 1.63 ± 0.58 | 1.59 ± 0.71 |
| **X-ray** | **stage I % (n)** | 18.54 (23) | 22.22 (6) | 17.52 (17) |
| | **stage II % (n)** | 39.51 (49) | 29.62 (8) | 42.26 (41) |
| | **stage III % (n)** | 28.22 (35) | 22.22(6) | 29.89 (29) |
| | **stage IV % (n)** | 13.70 (17) | 25.92 (7) | 10.30 (10) |
| **Duration of RA** | | 12.31 ± 8.09 | 13.70 ± 9.80 | 11.92 ± 7.56 |

*BMI – body mass index, RF – rheumatoid factor, ACPA – anti-citrullinated protein antibodies, DAS28 – disease activity score assessing 28 joints, HAQ – Health Assessment Questionnaire*

did not use any csDMARD because of contraindications or previous adverse reactions. Eighty-five patients (68.54%) used glucocorticoids as part of RA treatment. More than a fifth (20.96%) of patients was taking glucocorticoids at the time when they started bDMARD/tsDMARD therapy. The usual daily glucocorticoid dose was equivalent to 2.5–10 mg prednisone. Only one patient received a dose equivalent to 20 mg prednisone. No statistically significant differences were found in treatment with csDMARD and glucocorticoids between groups with and without LTBI (Table 2.).

The most frequently used biologics were TNFi (adalimumab, certolizumab pegol, etanercept, golimumab). Overall, this therapy was administered to 111 patients (89.51%). The second most commonly used bDMARD was tocilizumab (a monoclonal antibody against IL- 6 receptor, a-IL-6R) – 32.25% of patients were treated. Thirty-four patients (27.41%) were treated with two bDMARDs/tsDMARDs after previous treatment failure, and 13 patients (10.48%) required treatment with up to three or more drugs from this group (change for lack of effect or side effects) – Table 3.

The most common comorbidities were cardiovascular diseases (10 in LTBI+ve + vs 12 in LTBI-ve group), chronic obstructive pulmonary disease and pulmonary fibrosis (5 and 2 LTBI+ve vs LTBI-ve patients) and diabetes mellitus (7 patients in the LTBI+ve group).

LTBI was identified in 9 (7.25%) patients during treatment with csDMARD in combination with glucocorticoids, before initiation of bDMARD/tsDMARD treatment. These patients presented no clinical symptoms of TB, they had negative chest X-ray and positive IGRA test. Their TST diameter results were between 0–16 mm. During the treatment with biologics, LTBI was found in other 18 (14.51%) patients. 9 patients were diagnosed during treatment with tumor necrosis factor inhibitor (TNFi), 7 patients using anti-interleukin-6 receptor (anti-IL-6R) and 2 patients Janus ki-

**Table 2.** History of treatment with csDMARDs and systemic glucocorticoids

| | Previous treatment | | | Treatment at 1st LTBI screening | | |
|---|---|---|---|---|---|---|
| | Total (124) | LTBI+ve (27) | LTBI-ve (97) | Total (124) | LTBI+ve (27) | LTBI-ve (97) |
| **Methotrexate, % (n)** | 35.48 (44) | 40.74 (11) | 34.02 (33) | 60.48 (75) | 55.55 (15) | 52.41 (60) |
| **Leflunomide, % (n)** | 14.51 (18) | 14.81 (4) | 14.43 (14) | 14.51 (18) | 14.81 (4) | 16.49 (12) |
| **Hydroxychloroquine, % (n)** | 35.48 (44) | 40.74 (11) | 34.02 (33) | 10.48 (13) | 14.81 (4) | 14.43 (14) |
| **Sulfasalazine, % (n)** | 29.03 (36) | 37.03 (10) | 26.70 (26) | 4.03 (5) | 3.70 (1) | 4.14 (4) |
| **Cyclosporin, % (n)** | 8.87 (11) | 14.81 (4) | 7.21 (7) | 2.41 (3) | 0 | 3.09 (3) |
| **Oral corticosteroids** | 68.54 (85) | 66.66 (18) | 69.07 (67) | 20.96 (26) | 14.8 (4) | 22.70 (22) |

*LTBI+ve – positive screening for latent tuberculosis infection, LTBI-ve – negative screening for latent tuberculosis infection*

**Table 3.** Treatment with bDMARDs/tsDMARDs

| | Total (n = 124) | LTBI+ve (n = 27) | LTBI-ve (n = 97) | P-Value |
|---|---|---|---|---|
| **1 bDMARD/tsDMARD, %, (n)** | 55.64 (69) | 59.33 (16) | 54.65 (53) | 0.669 |
| **2 bDMARD/tsDMARD, %, (n)** | 27.41 (34) | 33.33 (9) | 25.77 (25) | 0.436 |
| **3 or more bDMARD/tsDMARD, %, (n)** | 10.48 (13) | 7.40 (2) | 11.34 (11) | 0.555 |
| **Treatment duration, y, average (min, max)** | 3.97 (0.5–19.0) | 4.59 (1–14) | 3.72 (0.5–8) | 0.115 |
| **TNFi, %, (n)** | 89.51 (111) | 66.66 (18) | 95.9 (93) | 0.001 |
| **a-IL-6R, %, (n)** | 32.25 (40) | 40.74 (11) | 29.89 (29) | 0.286 |
| **RTX, %, (n)** | 0.8 (1) | 3.7 (1) | 0 | 0.057 |
| **ABA, %, (n)** | 0.8 (1) | 0 | 1.03 (1) | 0.596 |
| **JAKi, %, (n)** | 14.51 (18) | 7.4 (2) | 16.49 (16) | 0.236 |

*bDMARDs – biologic disease modifying antirheumatic drugs , tsDMARDs – targeted synthetic disease modifying antirheumatic drugs, TNFi – tumor necrosis factor-a inhibitor, a-IL-6R – monoclonal antibody against IL-6 receptor, RTX – rituximab, ABA – abatacept, JAKi- Janus kinase inhibitor*

nase inhibitor (JAKi). The mean duration of treatment with bDMARD/tsDMARD, until LTBI was diagnosed, was 39.5 months (range 12–134 months). According to national recommendations, all positive for LTBI patients received prophylactic treatment with good adherence, and serious adverse effects did not occur. 26 patients were treated with isoniazid 300 mg daily during 6 months, one patient after 3 months isoniazid treatment was switched to rifampicin 600 mg daily because of elevated liver enzymes.

Follow-up QTF in LTBI treated patients tested after 12 month, for each patients showed persistent seropositivity except one case of seroreversion (conversion from positive to negative QTF). Active TB with clinical manifestation (TB of the knee) has occurred in one patient. Statistical analysis did not show an association between risk of LTBI and age, sex or treatment modality (Table 4).

**Table 4.** Relative risk of LTBI and potential risk factors

| | Value | 95% Confidence Interval | |
|---|---|---|---|
| | | Lower | Upper |
| **Sex female** | 0.48 | 0.132 | 1.761 |
| **Age ≥ 60** | 1.645 | 0.695 | 3.892 |
| **Age ≥ 65** | 1.562 | 0.540 | 4.514 |
| **BMI ≥ 30** | 0.763 | 0.235 | 2.481 |
| **RF** | 0.914 | 0.301 | 2.775 |
| **ACPA** | 1.145 | 0.379 | 3.461 |
| **Leflunomide** | 1.345 | 0.472 | 3.832 |
| **Hydroxychloroquine** | 1.645 | 0.695 | 3.892 |
| **Sulfasalazine** | 1.535 | 0.637 | 3.702 |
| **Cyclosporine** | 1.513 | 0.435 | 5.267 |
| **Glucocorticoids** | 0.798 | 0.328 | 1.945 |
| **Adalimumab** | 0.573 | 0.243 | 1.352 |
| **Etanercept** | 0.974 | 0.350 | 2.713 |
| **Golimumab** | 2.236 | 0.603 | 8.296 |
| **Certolizumab** | 0.951 | 0.288 | 3.144 |
| **Tocilizumab** | 2.407 | 1.003 | 5.780 |
| **Baricitinib** | 0.890 | 0.178 | 4.460 |
| **Smoking** | 0.633 | 0.170 | 2.356 |

*BMI – body mass index, RF – rheumatoid factor, ACPA – anti-citrullinated protein antibodies*

## DISCUSSION

Patients with rheumatic diseases are more likely to get LTBI than the general population due to immune system dysregulation and immunosuppressive therapy. In recent decades, treatment with bDMARDs and tsDMARDs has also become a part of therapy for resistant inflammatory rheumatic diseases as monotherapy or in combination with csDMARD or glucocorticoids. Recent targeted treatment includes TNFi, monoclonal antibodies against IL-6R, abatacept and rituximab, as well as synthetic targeted DMARDs tofacitinib and baricitinib. Randomized clinical and observational studies suggest a higher incidence of TB, particularly in patients treated with TNFi, as a result of the action of these drugs [8]. According to current recommendations, it is compulsory to screen patients for LTBI in the Slovak Republic before initiation of bDMARD/tsDMARD treatment as well as regular pneumological check-ups, including physical examination, TST, IGRA test and chest X-ray. However, some countries use different methods to prevent the spread of MT infection, which could be the reason for the different incidence of LTBI in both healthy and at-risk population of patients with rheumatic inflammatory diseases. It would be convenient for each country to have data about the LTBI prevalence in selected higher-risk population groups. LTBI treatment has been shown to reduce process activation by 65% [4]. The rate of successful treatment of TB in Slovakia is one of the highest in European countries (79.6% in 2017) [2]. There are some regimens recommended for treatment of LTBI by the Methodological Recommendation of the Chief Expert of the Ministry of Health of Slovak Republic: 6 month monotherapy of isoniazid, or 4 month monotherapy of rifampicin, or 3 month combination therapy of isoniazid and rifampicin [7]. Pneumologists choose the appropriate treatment based on the patient´s comorbidities and potentional drug-drug interactions.

Prior to discovering anti-cytokine treatment, several studies have highlighted an increased incidence of TB in RA patients. In a Spanish study by Carmona et al., the incidence risk ratio of pulmonary TB in RA patients was 3.68 (95% CI 2.36-5.92) compared to the general population [9]. Some studies have shown the evidence of 2-4 times higher risk of TB in RA patients without biological therapy [10, 11]. According to Canadian authors, the male population appears to be at higher risk [12]. Our results showed a non-significantly elevated prevalence of LTBI in women and older (60+ years) patients. Brassard et al. suggest a higher risk of LTBI associated with treatment with some csDMARDs (MTX and leflunomide) and glucocorticoids, especially for patients older than 65 [12]. So far, there is no clear data of LTBI association with methotrexate + glucocorticoid combination therapy. In the US population (4215 participants) LTBI prevalence was 5.0% [13]. In this study, LTBI was diagnosed in 7.25% of biologically naive patients. This incidence, close to the incidence found in the study of Martinez et al., does not mean a significantly higher risk of LTBI in RA, compared to the general population. Thus, identification of these

patients would be necessary to initiate anti-TB therapy and to prevent activation of infection to the clinical manifestation of TB infection [3].

Oral glucocorticoids (GC) were used in 20.96% of patients before starting anti-cytokine treatment in our study. GC may increase the risk of TB by interfering with immunoregulation, mainly due to the effect on the production of IL-1 and TNF, but also on cellular immunity. Jick et al. evaluated the risk of TB infection in patients treated with GC and found that relative risk TB was 4.9 (95% CI, 2.9–8.3) for dose equivalent to 15 mg prednisone per day, and up to 7.7 (95% CI, 2.8–21.4) at higher doses [14]. According to a statement from the American Thoracic Society and Centers for Disease Control and Prevention is GC therapy at a dose of prednisone ≥ 15 mg daily (or equivalent) for more than one month represents an increased risk of TB infection [15]. It is unclear whether the duration of treatment or the cumulative dose of corticoids affects the risk of TB. Cantini et al., suggest a higher incidence of TB in all patients with chronic GC use in the treatment of RA. However, a daily dose equivalent to 7.5 mg prednisolone appears to be low risk in the incidence of active TB [15].

Depending on the mechanism of action, biologics can be divided into two wide groups: TNFi and non-TNF targeted biologics. The risk of TB is 2–4 times higher in patients treated with TNFi than in the general population [16, 17]. The risk is higher in treatment with monoclonal antibodies (bind to both soluble and membrane-bound forms of TNF) than with TNFi binding soluble TNF receptor as etanercept. Different binding mechanisms are thought to be the cause of difference: while monoclonal antibodies (e.g., adalimumab, golimumab) bind to transmembrane TNF and induce T-cell apoptosis required to maintain granuloma integrity, etanercept as a soluble receptor does not have such activity. Another mechanism for potentiating TB is the inhibition of IFNγ by TNF inhibitors. Drugs without impact on TNF-related inflammation (e.g. abatacept, tocilizumab and rituximab) do not have this effect. Evaluations of the CORRONA (North America) multicentre registry records revealed a higher risk of TB in patients treated with MTX monotherapy, TNFi monotherapy and in combination therapy for these modalities [18].

Anti-IL-6R drugs (tocilizumab, sarilumab) from a group of non-TNF targeted biologics are well-known and often used in RA. A common side effect of these drugs is neutropenia that can lead to a higher incidence of bacterial infections. Opportunistic infections such as active TB or non-tuberculous mycobacterial infection were diagnosed less frequently. Japanese post-marketing observational study results suggest a similar risk of TB in patients treated with tocilizumab as with TNFi therapy. However, non-tuberculous mycobacterial infections were more frequent [19]. Rituximab and abatacept have shown a low risk of LTBI in several studies [15, 20]. According to Winthrop et al., the incidence of LTBI in patients treated with tofacitinib was low in regions with a low prevalence of TB. However, screening for LTBI is recommended before treatment initiation [19]. In general population pulmonary TB represents 80% of cases, while in RA patients treated with TNFi high prevalence of extrapulmonary TB was reported.

We also confirmed an increased incidence of LTBI in TNFi-treated patients (66.66% of all LTBI+ve patients), but in the tocilizumab group, we also found LTBI positive patients (40.74% of all LTBI+ve patients). The mean LTBI detection time since the initiation of bDMARD/tsDMARD was 39.5 months (12–134 months). These results confirm the necessity of LTBI screening and long-term monitoring in RA patients treated with any kind of bDMARD/tsDMARD. Anti-TB treatment of LTBI was given according to the Slovak national recommendations. There were no serious adverse reactions. All patients were compliant and completed chemoprophylactic therapy. A certain motivation could also be the effectiveness of RA treatment, which patients wanted to continue.

Jick et al. referred an association between TB risk and low body mass index (BMI), which meant a 3-fold increased risk of infection in patients receiving oral glucocorticoids regardless of underlying disease compared to the general population with normal BMI values [14]. The risk factor needs to be taken into consideration, as RA patients in the active stage of the disease are often underweight. However, the long duration of RA is more often associated with overweight and obesity. There was only one underweight patient in our study group. There was no significant difference in BMI between groups of LTBI-positive and -negative patients. The relationship between higher BMI/obesity and TB risk is complex. Higher body weight and obesity alone are associated with a significantly lower risk of TB. On the other hand, obesity (and also higher body weight) is an important risk factor for hyperglycemia and diabetes mellitus type 2 increasing the risk of TB [21].

The higher incidence of MT infection and active TB in RA patients is associated with the accumulation of comorbidities and patient´s risk behaviour [22]. In this study, the most common comorbidities were cardiovascular diseases (22 patients) with similar presentations in both groups. Alcoholism is also a risk factor for TBI, but there was not found excessive alcohol consumption in any patient.

Data on the prevalence of LTBI in the RA patient population are inconsistent because of different factors across countries: vaccination policy, incidence and prevalence of TB in the general population, prevention, screening of risk groups including RA patients, LTBI diagnosis methodology, LTBI treatment schedules, preference for different RA treatment modalities, etc. In areas with a high incidence and prevalence of TB, LTBI

was diagnosed in up to 33% of RA patients [23, 24]. The current treatment of RA may also affect the screening of MT infection. Hakimian et al. observed that high-dose corticosteroids may affect QFT-GIT outcomes leading to a high proportion of indeterminate results in a group of patients with RA and inflammatory bowel disease [25].

LTBI prevalence data in RA patient's population are not available in Slovakia. This work is the first study which maps the prevalence of LTBI in RA patients in our country and tries to identify the risk factors, especially associated with treatment modalities. LTBI was found in 21.77% of patients over the reporting period, mainly treated with TNFi. Only one patient was diagnosed with active TB in our study group (extrapulmonary form), which is an excellent result of active screening and prophylaxis of LTBI in these high-risk patients. LTBI prevalence before starting anti-cytokine treatment was low (7.25%) and close to general population prevalence, but during treatment was found in 21.7% of patients.

The main limitations of our study are the retrospective collection of data, the relatively small number of patients and the short time of the monitored period, which makes it impossible to assess the relative risk of individual groups of drugs.

## CONCLUSION

RA is associated with an increased risk of TB, but the incidence of clinically manifested TB in Slovakia is very low. Particular attention should be paid to patients with cumulative risk factors, and it is still a challenge to diagnose the disease with atypical manifestation correctly. RA treated with immunosuppressive agents presents an increased risk of developing TB, especially in patients treated with anti-cytokine therapy. Different degree of risk depends on the severity of the disease, treatment as well as the epidemiological situation of the country. The currently used recommendations are sufficiently sensitive to identify MT infection in patients treated with bDMARDs/tsDMARDs. There remains a question of screening and prophylactic TB therapy of patients treated with csDMARDs in combination with glucocorticoids. However, due to the low risk ratio of LTBI progression to clinically manifest TB and toxicity of chemoprophylaxis, there is still insufficient data to support LTBI screening in this group of patients in countries with low TBI prevalence.

Risk assessment of TB in immunocompromised patients is still a significant problem that requires cooperation with local experts in epidemiology and pneumology. The epidemiological situation may be different from country to country due to different regional prevention regulations and the possible impact of migration on disease incidence.

## REFERENCES


1. WHO. Global tuberculosis report 2018, Geneva: World Health Organization 2018. ISBN 978-92-4-156564-6, 265 p.
2. https://www.ecdc.europa.eu/en/publications-data/country-profile-slovakia-5.
3. WHO. Latent tuberculosis infection: updated and consolidated guidelines for programmatic management. Geneva: World Health Organization 2018, 64 p. ISBN 978-92-4-155023-9.
4. Vuorela M, Mars NJ, Salonen J, Kauppi MJ. Tuberculosis in people with rheumatic disease in Finland 1995–2007: a nationwide retrospective register study. *Rheumatol Adv Pract*, 2019; 3(2): rkz020. doi: 10.1093/rap/rkz020. PMCID: PMC6736076; PMID: 31528842.
5. Safiri S, Kolahi AA, Hoy D, et al. Global, regional and national burden of rheumatoid arthritis 1990–2017: a systematic analysis of the Global Burden of Disease study 2017. *Ann Rheum Dis*, 2019;78(11):1463–1471.
6. Shin A, Shin S, Kim J, Ha Y-J, et al. Association Between Socioeconomic Status and Comorbidities Among Patients With Rheumatoid Arthritis Results of a Nationwide Cross-Sectional Survey. *Rheumatology*, 2019;58(9):1617–1622.
7. Hájková M, Solovič I. Metodické odporúčanie hlavného odborníka MZ SR o štandardizácii diagnostiky latentnej tuberkulóznej infekcie, 27.1.2017.
8. Homolka J. Risk of tuberculosis in patients treated with biological medicines. *Bratisl Med J*, 2016;117(1):11–14.
9. Carmona L, Hernández-García C, Vadillo C, et al. Increased risk of tuberculosis in patients with rheumatoid arthritis. *J Rheumatol*, 2003;30(7):1436–1439.
10. Arkema EV, Jonsson J, Baecklund E, et al. Are patients with rheumatoid arthritis still at an increased risk of tuberculosis and what is the role of biological treatments? *Ann Rheum Dis*, 2015;74(6):1212–1217.
11. Askling J, Fored CM, Brandt L, et al. Risk and case characteristics of tuberculosis in rheumatoid arthritis associated with tumor necrosis factor antagonists in Sweden. *Arthritis Rheum*, 2005;52(7):1986–1992.
12. Brassard P, Lowe AM, Bernatsky S, et al. Rheumatoid arthritis, its treatments, and the risk of tuberculosis in Quebec, Canada. *Arthritis Rheum*, 2009;61(3):300–304.
13. Martinez L, Zhu L, Castellanos ME, et al. Glycemic Control and the Prevalence of Tuberculosis Infection: A Population-based Observational Study. *Clin Infect Dis*, 2017;65(12):2060–2068.
14. Jick SS, Lieberman ES, Rahman MU, Choi HK. Glucocorticoid use, other associated factors, and the risk of tuberculosis. *Arthritis Rheum*, 2006;55(1):19–26.
15. 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.
16. Baronnet L, Barnetche T, Kahn V, et al. Incidence of tuberculosis in patients with rheumatoid arthritis. A systematic literature review. *Joint Bone Spine,* 2011;78(3):279–284.
17. Souto A, Maneiro JR, Salgado E, et al. Risk of tuberculosis in patients with chronic immune-mediated inflammatory diseases treated with biologics and tofacitinib: a systematic review and meta-analysis of randomized controlled trials and long-term extension studies. *Rheumatology* (Oxford), 2014;53(10):1872–1885.
18. Greenberg JD, Reed G, Kremer JM, et al. CORRONA Investigators. Association of methotrexate and tumour necrosis factor antagonists with risk of infectious outcomes including opportunistic infections in the CORRONA registry. *Ann Rheum Dis*, 2010;69(2): 380–386.
19. Winthrop KL, Mariette X, Silva JT, et al. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Soluble immune effector molecules [II]: agents targeting interleukins, immunoglobulins and complement factors). *Clin Microbiol Infect*, 2018;24(Suppl 2):S21–S40.
20. Mease PJ, Gottlieb AB, van der Heijde D, et al. Efficacy and safety of abatacept, a T-cell modulator, in a randomised, double-blind,

placebo-controlled, phase III study in psoriatic arthritis. *Ann Rheum Dis*, 2017;76(9):1550–1558.
21. Lin HH, Wu CY, Wang CH, et al. Association of Obesity, Diabetes, and Risk of Tuberculosis: Two Population-Based Cohorts. *Clin Infect Dis*, 2018;66(5):699–705.
22. Dougados M, Soubrier M, Antunez A, et al. Prevalence of comorbidities in rheumatoid arthritis and evaluation of their monitoring: results of an international, cross-sectional study (COMORA). *Ann Rheum Dis*, 2014;73(1):62–68.
23. Anton C, Soubrier M, Antunez A, et al. Latent tuberculosis infection in patients with rheumatic diseases. *J Bras Pneumol*, 2019;45(2):e20190023. doi: 10.1590/1806-3713/e20190023. PMCID: PMC6733747. PMID: 31038654.
24. Song GG, Bae SC, Lee YH. Interferon-gamma release assays versus tuberculin skin testing in patients with rheumatoid arthritis. *Int J Rheum Dis*, 2013;16(3):279–283.
25. Hakimian S, Popov Y, Rupawala AH, et al. The conundrum of indeterminate QuantiFERONTB Gold results before anti-tumor necrosis factor initiation. *Biologics*, 2018; 12(1):61–67.

*Do redakce došlo dne 6. 6. 2020.*

*Adresa pro korespondenci:*
***doc. MUDr. Emőke Šteňová, Ph.D.***
*I. interná klinika LF UK a UNB*
*Mickiewiczova 13*
*813 69 Bratislava*
*Slovakia*
*e-mail: e.stenova@hotmail.com*