Marija Laban Lazović[1] Ana Blanka[1] Tatjana Adžić-Vukičević[1,2]
Marina Đikić[3] Nikola Trboljevac[1]

DIFFERENT FORMS OF MYCOBACTERIAL INFECTIONS IN PATIENTS RECEIVING ANTI-TNF THERAPY – CASE REPORTS

Abstract: Biological agents, including TNF-alpha antagonists, have been used in treatment of autoimmune diseases for over 20 years. Due to impaired T-cell immunity and blocked effects of TNF-alpha mediator, patients receiving this therapy have increased risk of developing tuberculosis or other non-tuberculous mycobacterial infections. Both tuberculosis and other mycobacterial infections may occur anytime in patients who have ever used these medicines, even after the first injection. Most often we see activation of latent tuberculosis confirmed by screening tests. IGRA tests (QuantiFERON and T-SPOT.TB) are significantly more sensitive and specific for testing population of immunosuppressed patients, in comparison to tuberculosis skin test. There are contemporary recommendations for diagnosing, monitoring, chemoprophylaxis and treatment of latent and active tuberculosis in adults and children in case of planning administration of TNF-alpha antagonists or in cases when these drugs have already been used. Prevention of active tuberculosis via diagnosing LTBI and use of chemoprophylaxis is the crucial component of the strategy of World Health Organization for elimination of TB (End TB Strategy).

Key words: tuberculosis, TNF-alpha antagonists, IGRA test, chemoprophylaxis

Introduction

Tumor necrosis factor- alpha (TNF- alpha), interleukin 12 (IL 12) and interferon gamma (IF gamma) are the most significant mediators taking part in protection from

[1] Marija Laban Lazović, Clinic for Pulmonology, University Clinical Center of Serbia, e-mail: marija.labanlazovic@gmail.com

[2] Faculty of Medicine, University of Belgrade

[3] Emergency Center, University Clinical Center of Serbia

intracellular infections, particularly mycobacterial infections. The most important among them is TNF-alpha, playing crucial role in the inflammatory response and granuloma formation. Biological agents, including TNF-alpha antagonists, have been used in treatment of autoimmune diseases, above all for treatment of rheumatoid and psoriatic arthritis, ulcerative colitis and Crohn`s disease, for over 20 years. This kind of agents is mostly used after the failure of corticosteroids or other immunosuppressant drugs. Due to impaired T-cell immunity and blocked effects of TNF-alpha mediator, patients receiving this therapy have increased risk of developing tuberculosis or other non-tuberculous mycobacterial infections (1). Duration of anti-TNF-alpha therapy is of no relevance for developing infections. Both tuberculosis (TB) and other mycobacterial infections (NTMB) may occur anytime in patients who have ever used these medicines, even after the first injection (2). Most often we see activation of latent tuberculosis (LTBI), confirmed by screening tests (3). Beside pulmonary, very often we see extrapulmonary tuberculosis in form of tuberculous lymphadenitis, pleuritis and peritonitis, as well as forms of miliary tuberculosis, particularly with use of infliximab (2). Mycobacterial infections often do not cause expected respiratory problems, but generalized difficulties such as fatigue, sweating and fever, and must not be related to the primary disease, especially because biological agents efficiently alleviate symptoms of primary disease. There are contemporary recommendations for diagnosing, monitoring, chemoprophylaxis and treatment of latent and active tuberculosis in adults and children in case of planning administration of TNF-alpha antagonists or in cases when these drugs have already been used (4).

Presentation of cases

We will present the cases of three patients treated at the Clinic for Pulmonology of the Clinical Center of Serbia, who received biological therapy of TNF-alpha antagonists and developed different forms of mycobacterial infections.

Case 1

Female, T. D., 60 years old, a nurse, transferred from the Clinic for Infectious and Tropical Diseases of the Clinical Center of Serbia, where she was examined and treated for a month because of fever of unknown origin. After the vaccine against smallpox, at the age of 20, she developed psoriasis and psoriatic arthritis and ever since received different therapies. Until the age of 58 she was refusing suggested immunosuppressant therapy and was treated with non-steroid anti-inflammatory drugs, but did use, frequently and on her own, corticosteroid depot ampoules ”Diprofos“). Due to progressive joint pain, she received metotrexat for 6 months, but with no effect

and with pronounced side effect of lower legs swelling. Therefore, this treatment has stopped and she agreed to receive biological therapy of TNF-alpha antagonists (infliximab – ”Remicade“). First injection she tolerated well. After the second one (two weeks after the first dose), she developed high fever, up to 40°C, with chills, shivering and malaise. There were no respiratory symptoms. Detailed diagnostics were completed at the Clinic for Infectious and Tropical Diseases CCS, which excluded suspected bacterial and viral causes of fever. Additional immunological analyses, thyroid tests and tumor markers showed no irregularities. PA radiography verified fibrous changes of voluminous hilums, and thoracic CT showed bilateral, diffuse, micronodular miliar changes of the lung parenchyma. The anamnesis of this patient included arterial hypertension and smoking.

When admitted to the Clinic for Pulmonology of the Clinical Center of Serbia, she was very pale, with temperature of 38,8°C, mild dyspnea, without cyanosis, hemodynamically stable, of gracile osteomuscular constitution, with regular physical findings of heart and lungs. Examination revealed enlarged, soft supraclavicular lymph node on the right, and skin erythema above psoriatic changes and ulnar deviations of hands and feet. Laboratory findings verified severe inflammatory syndrome (SE 100, CRP 100) and microcytic anemia (HGB 81, MCV 75, Fe 3), while gas analysis showed hypoxia (PO2 8,5 Kpa). Acido-alcohol resistant bacillus (ARB) was not found in sputum and bronchial aspirate, and Loewenstein cultures (LOW K) of sputum, aspirate, blood and urine remained negative. Urine culture, blood culture and sputum and bronchial aspirate bacteriological cultures were sterile, and broader virological tests (including HIV) were negative. Tuberculosis skin test (PPD) triggered pronounced positive reaction. Abdominal ultrasound showed hepatosplenomegaly. Biopsy of supraclavicular lymph node led to pathohystological finding of granulomatous lymphadenitis ***Lymphadenitis granulomatosa vs. Tuberculosis caseoproductiva***. Bronchoscopic finding indicated inflammation, while pathohystological finding of transbronchial biopsy was non-specific (”bronchitis chronica“). After pathohystological finding in the biopsied lymph node, but also due to radiographic finding of miliary RB, anti-TB therapy was introduced (H- Isoniazid 300mg, R-Rifampicin 600mg, Z- Pyrazinamid 1200mg and E- Etambutol 1200mg). Patient tolerated this therapy well, with good laboratory findings, fast improvement of inflammatory syndrome, anemia and clinical improvement as well. Outpatient treatment was continued at the City Institute for Pulmonary Diseases in Belgrade, with the recommendation of administering therapy for 6 months, according to the protocol for extrapulmonary and miliary tuberculosis (two months of HRZE, four months HR). Treatment was completed with special efforts of home-care personnel, since the patient was in no mood for regular check-ups, nor did she respond to phone calls and attempts of home-care service to reach her. A bit over 7 months after the beginning of anti-TB therapy, treatment was officially over, with the complete radiographic regression and reduction of the previously enlarged

supraclavicular lymph node, and the patient was discharged as cured. We have no knowledge on further treatment of psoriasis and psoriatic arthritis.

Case 2

Patient A. S., age 43, admitted to the Clinic for Pulmonology of the Clinical Center of Serbia for the first time when she was transferred, due to suspected miliary tuberculosis, from the Clinic for Gastroenterology and Hepatology of the Clinical Center of Serbia, where she was treated for 3 years already for Crohn`s disease. Diagnosis of Crohn`s disease was reached by small intestine biopsy, when during routine cholecystectomy a conglomerate of enlarged lymph nodes was found at the level of terminal ileum, as well as entero-enteral fistula. Resection of terminal ileum was performed, with ileocecal anastomosis. Treatment of Crohn`s disease began with mesalazine and colestyramin, leading to short-term remission of the disease. In further treatment were used corticosteroids and immunosuppressant's, but despite the therapy, symptoms of the disease persisted on anostomosis. Prevailing clinical features were alternating diarrhea and suboclusive disorders. Next step in treatment was biological therapy of TNF-alpha antagonists (infliximab – "Remicade"). Patient tolerated initial two injections well, and gastrointestinal discomfort was significantly reduced. But after the third injection (6 weeks after the first), she developed fever up to 40°C, with chills, shivering, sweating and extreme malaise. There were no respiratory difficulties. Colonoscopy and esophagogastroduodenoscopy eliminated reactivation of Crohn`s disease. Abdominal ultrasound was regular. Chest radiography, which showed no changes before, verified bilateral diffuse micronodular miliary shadows. Thoracic CT confirmed miliary changes of lung parenchyma, hilar and mediastinal lymphadenopathy, and pleural effusion on the right side. The largest lymph node conglomerate was subcarinal – 33x30 mm. In her anamnesis the patient denied having any chronic disease, except for depressive syndrome, and stated she used to smoke.

She was admitted to the Clinic for Pulmonology of the Clinical Center of Serbia with fever of 38.5°C, pale, eupneic at rest, non-cyanotic, with no peripheral lymphadenopathy, and in very depressed mood. Physical findings of heart and lungs were regular. Laboratory findings verified inflammation (CRP 168, SE 64) and mild microcytic anemia (Hgb 102, MCV 80). There were no gas exchange disorders in arterial blood. No acido-alcohol-resistant bacilli were found in sputum and bronchial aspirate, and Loewenstein cultures of sputum, bronchial aspirate, urine and blood were negative. Virological and further immunological analyses, as well as hormonal thyroid analyses were normal. Bronchoscopy verified widening of the main carina and transcarinal biopsy was performed. Pathohystological finding was non-specific ("bronchitis chronica"). Based on the risk factors, clinical picture, radiographic and CT findings, it was decided, due to suspected miliary TB, to begin quadruplet anti-TB

treatment (H – Isoniazid 300mg, R- Rifampicin 600mg, Z- Pyrazinamide 1200mg, E- Ethambutol 1200mg). The therapy was tolerated well. At the first check-up, two months after the therapy started, there was a significant regression of changes of lung parenchyma, and at the end of six-month anti-TB treatment complete regression of all changes was achieved. The continuation phase of treatment lasted for four months, as recommended, and included two drugs (H 300mg, R 600mg). Then this six month treatment was declared completed and patient was discharged. Along with anti-TB therapy, the patient used immunosuppresants (azathioprine) as recommended by gastroenterologist. But only a month after completing anti-TB treatment, general symptoms recurred. Dominant symptom was high temperature. Primary gastrointestinal disease was evaluated and possibility of reactivation was excluded. Thoracic and abdominal CT verified *de novo* lympadenopathy, enlarged supraclavicular lymph node on the right and splenomegaly, which was registered by the physical exam as well. Treatment of Crohn`s disease was continued with mesalazine, again, and without azatioprin. Biopsy of the supraclavicular lymph node was performed. Pathohystological finding confirmed granulomatous specific lymphadenitis ***(Lymhadenitis granulomatosa vs. Tuberculosis fibrocaseosa*)**. Laboratory analyses registered mildly elevated inflammation parameters, and chest radiography showed wider upper mediastinal shadow due to mediastinal lymphadenopathy, with no changes in lung parenchyma. After detailed hematologic examination, nothing pointed toward lymphoproliferative diseases. Bronchologic examination was not repeated. Second opinion of the pathologist was obtained, related to biopsy from intestinal surgery, and it confirmed the diagnosis of Crohn`s disease and excluded intestinal tuberculosis. Anti-TB treatment in accordance to the retreatment regimen was initiated (H 300mg, R 600mg, E 1200mg, Z 1200mg, S- Streptomycin 1g (im)). Along with it the patient received mesazaline. Outpatient treatment of tuberculosis was continued, in accordance with the regimen: two months of HRZES, one month of HRZE, 5months of HRE. Clinical status of the patient was good all along, with no respiratory and no gastrointestinal difficulties, and with no lymphadenopathy. Treatment of tuberculosis lasted for 8 months and was successfully completed. Patient was discharged, had several routine pulmonary check-ups later on, without findings of new pulmonary changes, and follow-up Loewenstein cultures were negative.

Case 3

Patient K. D., aged 60, treated for 15 years for seropositive rheumatoid arthritis (RA) with corticosteroids and metotrexate, and for the last two years receiving biological drug from the group of TNF-alpha antagonists (etanercept – ”Enbrel“). Also suffering from chronic obstructive lung disease. Pulmonary examinations started because of persistent cough, night sweats and painful arms and shoulders. On outer

side of both upper arms and, also bilaterally, in the shoulder region (m. deltoideus), for a whole year he had persistent solid livid exulcerated tumefactions which could not heal despite intense antibiotic therapy he received both outpatient and in hospital. The cause of skin changes was not determined despite repeated bacteriological and mycological analyses. Biopsy was not performed. PA chest radiography verified lighter parts of lower part of the right lung, and thoracic CT, particularly focused on shoulder bones, showed fibronodular and cavitary changes of the lower lobes of both lungs, as well as soft-tissue tumefactions laterally to both humeruses, with erosion of humeral heads and effusion of both shoulder joints. Sputums obtained via outpatient procedures were directly negative for acido-alcohol-resistant bacilli, and only in one Loewenstein culture was identified Mycobacterium xenopi. Due to respiratory difficulties, worsened rheumatological disease and sputum finding, the patient was admitted to the Clinic for Pulmonology, Clinical Center of Serbia.

He was admitted as hardly mobile on his own, due to rheumatoid arthritis, with no fever, dyspneic, cyanotic, pale, hemodynamically stable. Lung auscultation registered inspiratory crackles over lung bases, while heart findings were normal. Severe deformities like ulnar deviations were verified on all extremities, and in deltoid regions were found exulcerated tumefactions up do 10x10cm, with serohemorrhagic secretions. Laboratory analyses found higher SE (86) and mild normocytic anemia (HGB 100, MCV 82), while all other parameters, including CRP, were within referent ranges. Virological analyses, including HIV test, were negative. Out of eight sputums left to be analyzed at the Clinic for Pulmonology, in six was identified Mycobacterium xenopi (over 200 colonies per sputum). In three sputums ARB were directly verified. Wound swab and culture of tumefactions` content were bacteriologically and mycologicaly sterile. Loewenstein cultures of content of tumefactions remained negative after eight weeks. Incision of the change in the region of right deltoid muscle led to pathohystological finding of caseous necrosis.

In accordance with the ATS (American Thoracic Society) guidelines, the treatment began with two anti-TB drugs (rifampicin, ethambutol) and a macrolid (clarithromycin). Since M. xenopi was verified only in one Loewenstein sputum culture taken through outpatient procedure, and because of the possibility that direct positive microscopies reveal infection caused by TB bacillus, while waiting for the results of Loewenstein cultures obtained in hospital, izoniazid and pyrazinamide were also included. The plan was to correct the therapy after identification of the cause. Patient had severe pains in extremities and spine all the time so, in consultations with rheumatologist, he also received parenteral corticosteroids and painkillers. He was discharged, to continue therapy at home, but month and a half after initiation of anti-mycobacterial treatment, his state severely deteriorated, including suffocations. He was instantly readmitted, the same day, to the Clinic for Pulmonology CCS, where he died several hours later. Findings of clinical autopsy determined that cause of death

was a specific disease - granulomatous pneumonia with abscesses, while findings on his heart indicated granulomatous myocarditis. Pathologist noted it was a disseminated form of M. xenopi mycobacterial infection, and that was the first confirmed case of lethal outcome of disseminated mycobacteriosis in our country.

Discussion

Three different cases presented complications of anti-TNF treatment such as severe mycobacterial infections – cases of two forms of TB – miliary and TB lymphadenitis in patients treated with infliximab and a case of disseminated mycobacteriosis with lethal outcome in patient receiving etanercept.

Infliximab is the most potent TNF-alpha antagonist, carrying high risk of tuberculosis, primarily as a consequence of latent TB in countries with high and moderate seroprevalence to tuberculosis, such as Serbia (2). Anti-TNF antagonists are used in treatment of rheumatic and psoriatic arthritis, psoriasis, Crohn`s disease and ulcerative colitis, usually after failure of treatment with corticosteroids and immunosuppressants or because of resistance to these drugs (5). Blocking the effect of TNF-alpha mediators interferes with the crucial role of preventing tuberculosis and infections with non-TB mycobacteria. Efficiency in alleviating symptoms of the primary disease is significant, but the risk of mycobacterial infection is high and always present, regardless of the moment of initiating or discontinuing biological treatment. Similarly, there is high risk when it comes to adalimumab. Infliximab and adalimumab belong to the group of ”mabs“, monoclonal antibodies that bind specifically to TNF-alpha (6). Etanercept belongs to the group of „cepts“, fusion proteins fusing soluble TNF receptor to the constant end of IgG1 antibodies. Tuberculosis develops soon after initiation of therapy with TNF-alpha antagonists. When infliximab is used, almost in half of cases TB occurs within the first 90 days (12 weeks) since the beginning of therapy, which most probably indicates the reactivation of LTBI (7). TB infection following etanercept treatment occurs less often and later on in the treatment in comparison with infliximab and adalimumab. There are different forms of possible mycobacterial infections. Usually it is lung tuberculosis, but extrapulmonary forms, miliary lung or generalized tuberculosis are also common, as well as non-tuberculous mycobacteria (NTMB) – which are rarely suspected (8). Apart from the use of infliximab, the first patient was also at risk because of uncontrolled use of depot corticosteroids which are still often used for their fast and successful alleviation of rheumatic symptoms, and are most often used by patients on their own, with no doctor`s prescription or supervision. In case of second patient it was about LTBI reactivation following infliximab treatment. Duration and protocol of treating miliary TB was fully realized according to guidelines (two months- Isoniazid, Rifampicin, Pyrazinamide, Ethambutol (HRZE) and 4 months -Isoniazid, Rifampicin (HR)- 6 months in total). Additional risk factors

for further development of TB lymphadenitis was the use of immunosuppressant therapy along with anti-TB medication, which was necessary because of the active Crohn`s disease. But azathioprine was excluded as soon as recidivant TB was suspected. Third case, the first registered lethal outcome of disseminated Mycobacterium xenopi infection in HIV negative patient receiving etanercept treatment. As already underlined, use of etanercept carries significantly smaller risk of TB in comparison with infliximab, and non-TB mycobacteria, especially generalized infections, are rarely seen in practice (9). All three patients, otherwise HIV-negative, were initially on long-term immunosuppressive therapy, and due to disease resistance or side effects, anti-TNF therapy was introduced (10). General symptoms were prevalent in all patients, and infections after the use of TNF-alpha antagonists developed quickly and dramatically.

Therefore most countries introduced screening and treatment of latent tuberculosis (LTBI) prior to biological treatment, primarily with drugs belonging to the group of TNF-alpha antagonists, in order to reduce the incidence of active TB in these patients. Lack of screening, for the purpose of identifying LTBI and preventing active TB through chemoprophylaxis, leads to significantly higher incidence of the disease in patients receiving anti-TNF therapy (4). Accordingly, if a patient who should receive anti-TNF therapy has no symptoms indicating active TB, it is necessary to perform screening tests in order to eliminate the possibility of latent TB.

Methods to diagnose LTBI include tuberculosis skin test (PPD) and IGRA tests (11). IGRA tests are most commonly recommended. These tests alone cannot distinguish latent from active TB, but it is the only way to select persons who would benefit from chemoprophylaxis, after performing other additional examinations. A person with LTBI has no symptoms and is not contagious, her chest radiography shows no irregularities, microscopy and Loewenstein cultures are negative, but PPD and/or IGRA tests are positive. A person with active TB has manifested disease, symptoms of infections, is contagious, PPD or IGRA are usually positive, chest x-ray usually shows pathological changes, and direct microscopy or Loewenstein cultures are – in pulmonary forms – usually positive. Treating active TB is compulsory. Chemoprophylaxis includes use of one anti-TB drug (Isoniazid 300mg for 6 to 9 months), but there is also another regimen of simultaneous use of two anti-TB drugs (Isoniazid 300mg, Rifampicin 600mg, for 3 months, which is less often used because it is not tolerated so well or Rifampicin 600mg for 4 months).

None of our three patients underwent LTBI screening initially, nor did they get chemoprophylaxis. At the time their treatments were initiated, LTBI screening was not compulsory, as it is today. Lack of chemoprophylaxis is the main cause of developing active TB infection in all patients. Adoption of Guidelines for Diagnosing Latent Tuberculosis, issued by the Clinic for Pulmonology, Clinical Center of Serbia and Serbian Respiratory Society, updated in 2019, harmonized standards in sense that

screening is recommended both for active and latent TB prior to initiating anti-TNF therapy (4). Apart from anamnesis, physical examination and chest radiography, it is required to test samples to ARB and Loewenstein cultures, and to perform screening tests including tuberculosis skin test PPD and/or IGRA tests (QuantiFERON TB GOLD and T-SPOT.TB) – and latter are significantly more sensitive and specific in case of immunosuppressed patients in comparison with PPD. Crucial questions in anamnesis refer to previous treatments of active or LTBI, symptoms of active TB and BCG vaccination. In patients previously adequately treated for active TB, chemoprohylaxis is not used, except if there are clear indicators of high possibility of reinfection (4). Anti-TNF therapy can start 4 weeks after chemoprophylaxis. Further on, biological therapy and chemoprohylaxis can be used simultaneously. It is recommended for patients using anti-TNF therapy to have pulmonary evaluation and chest radiographies every 3 months, exactly because possible occurrence of active tuberculosis. Developing TB during use of anti-TNF therapy cannot be completely prevented, in spite of use of chemoprophylaxis with 60–90% efficiency. In such cases it is necessary to treat active TB with complete treatment regimen, as well as to discontinue anti-TNF therapy immediately. If anti-TNF treatment is necessary, it can be continued after completing initial phase of TB treatment, but only if it is not the miliary form of TB. But the best would be to replace TNF-alpha antagonist with biological drugs which mechanisms of action are different, such as tocilizumab or rituximab.

Conclusion

Anti-TNF therapy is an important risk factor for developing severe, disseminated and extrapulmonary forms of tuberculosis and mycobacterioses. TB and mycobacterioses must always be suspected in long lasting generalized or respiratory symptoms in patients receiving anti-TNF therapy. Following guidelines for screening and treatment of latent and active tuberculosis reduces frequency of the disease in patients using immunosuppressive therapy, and especially TNF-alpha antagonists. IGRA tests (QuantiFERON and T-SPOT.TB) are significantly more sensitive and specific for testing population of immunosuppressed patients, in comparison to tuberculosis skin test. These tests are the only way to identify patients who would have benefited from the chemoprophylaxis among patients asymptomatic before the initiation of anti-TNF therapy (12). Anti-TNF therapy is contraindicated in cases of active TB and cases of confirmed LTBI require chemoprophylaxis. Prevention of active tuberculosis via diagnosing LTBI and use of chemoprophylaxis is the crucial component of the strategy of World Health Organization for elimination of TB (End TB Strategy).

Literature

1. Zheng Zhang, Wei Fan, Gui Yang, Zhigao Xu, June Wang, Qingyuan Cheng Mingxia Yu. Risk of tuberculosis in patient treated with TNF-alfa antagonist: a systematic review and meta-analysis of randomised controlled trials. 2017 Mar 22; 7(3): e012567. doi: 10.1136/bm jopen-2016-012567.
2. J Keane, S Gershon, R P Wise, E Mirabile- Levens, J Kasznica, W D Schwieterman, J N Siegel, M M Braun. Tuberculosis associated with infliximab, a tumor necrosis factor alpha- neutralizing agent. N Engl J Med. 2001 Oct 11; 345 (15): 1098–104. doi: 10.1056/NEJMoa011110.
3. Schlovinck E, Wilkinson KA, Whelan AO, et al. Gamma interferon- based immunodiagnosis of tuberculosis: comparison between whole-blood and enzyme linked immunospot methods. J Clin Microbiol 2004; 42: 829–31.
4. Vučinić Mihailović V, Stošić M, Popadić D, Damjanov N, et al. Latent Tuberculosis - Guidelines for Diagnosing Latent Tuberculosis With Examples From the Practice. Clinic for Pulmonology of the Clinical Center of Serbia, Respiratory Society of Serbia, Belgrade, 2019.
5. Soumajyoti Sarkar, Saumya Panda, Byungsoo Kim, Smriti K, Raychaudhuri, Asutosh Ghosh, Siba P Raychaudhuri. Risk of tuberculosis with anti-tumor necrosis factor-alpha therapy in patients with psoriasis and psoriatic arthritis in Indian population. Indian Journal of Dermatology,Venerology and Leprology. Pub Date2 019-11-14. doi: 10.4103/ijdvl.ijdvl_791_18.
6. Maria Sofia Castelli, Paul Mc Gonigle, Pamela J. Hornby- The pharmacology and therapeutic applications of monoclonal antibodies. Pharmacol Res Perspect. 2019 Dec; 7(6): e00535. doi: 10.1002/prp2.535.
7. Soni Parita, Kumar Vivek, Kamholz Stephan, Pascal William, Kupfer Yizhak. Infliximab Therapy Leding to Pulmonary Tuberculosis in a Patient With Negative Interferon gamma Release Assay (IGRA)- Based QuantiFERRON Gold Test. J Investig Med High Impact Case Rep. 2017 Jul-Sep; 5(3): 2324709617717540. doi: 10.1177/2324709617717540.
8. Dmitriy Kedrin, Ricard Masia, Rosalynn M. Nazarian, John J. Garbe. Mycobacterium chelonae Bacteremia After First Dose of Infliximabe for Ulcerative Colitis. Am J Gastroenterol. 2014 Sep; 109(9): 1501–1502. doi: 10.1038/ajg.2014. 209.
9. Shunsuke Mori, Hitoshi Tokuda, Fumikazu Sakai, Takeshi Johkoh, Akio Mimori, Norihiro Nishimoto, Sadatomo Tasaka, Kazuhiro Hatta, Hidekazu Matsushima, Shunji Kaise, Atsushi Kaneko, Shigeki Makino, Seiji Minota, Takashi Yamada, Shinobu Akagawa, Atsuyuki Kurashima, and the NTM-BIORA (NTM infection in Biologic-treated RA patients) Study Investigators. Radiological features and therapeutic responses of pulmonary nontuberculous mycobacterial disease in rheumatoid arthritis patients receiving biological agents: a retrospective multicenter study in Japan. Mod Rheumatol. 2012 Sep 22(5): 727–737. doi: 10.1007/s10165-011-0577-6.
10. Lorenzetti R, Zullo A, Ridola L, et al. Higher risk of tuberculosis reactivation when anti-TNF is combined with immunosuppressive agents: a systematic review of randomized controlled trials. Ann Med 2014; 46(7): 547–554.

11. World Health Organization (2018). Latent tuberculosis infection: updated and consolidated guidelines for programmatic management. Geneva: World Health Organization.
12. John- Leonardo Torres- Castiblanco, Jorge Alberto Carrillo, Daniel Hincapie- Urrego, Adriana Rojas- Villarraga. Tuberculosis in era of anti- TNF alpha therapy: Why does the risk still exist? Biomedica. 2018 Mar 15; 38(1): 17–26. doi: 10.7705/biomedica.V38i0.3458.