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Incidence of latent tuberculosis in rheumatic diseases after taking immunesuppressive drugs

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Tuberculosis remains a serious public health concern. Comorbidity in immunocompromised patients makes its diagnosis more difficult. The present study was conducted to assess the prevalence of positive tuberculin skin test and Chest X-ray changes in patients with rheumatologic diseases treated with immunosuppressive medications in the city of Birjand, Iran. The present prospective study was conducted in 2020 in the city of Birjand, Iran on 40 patients with rheumatologic diseases and 40 healthy people. Inclusion criteria were patients with the diagnosed rheumatic disease under treatment with immunosuppressive drugs. Exclusion criteria were active tuberculosis and changes in chest X-ray in favor of tuberculosis. Purified protein derivative solution was used to carry out a tuberculin skin test and screen both groups for latent tuberculosis and Chest X-ray to ascertain the presence or absence of the radiographic signs of old tuberculosis in the patients' group at the initiation of treatment and six months after. The collected data were recorded in a checklist and then analyzed in SPSS-22 using descriptive and statistical tests. Mean age was 47.32 ± 13.61 years in the case group and 46.40 ± 14.19 years in the control. Also, 7.5% of the case group patients taking immunosuppressive medications were tuberculin skin test positive, but no significant difference was observed between the case and control groups (*P value* = 0.24). In the positive tuberculin skin test group, 66.6% had spondyloarthritis of whom, 100% were taking Cinnora (Adalimumab). The emergence of latent tuberculosis in rheumatic patients after taking immunosuppressive medications is likely, and clinicians should be aware of its risk.

Keywords: Tuberculosis; Mycobacterium Tuberculosis; Tuberculin skin test; Rheumatic disease; Immunosuppressive medication

Introduction

Patients with the rheumatic disease are at risk of infection due to the immunosuppressive effect of the drug and immune system dysfunction as a result of the disease [1]. Over the past two decades, there has been a greater use of synthetic and biologic Disease Modifying Anti Rheumatic Drugs (DMARDs) to control rheumatic diseases. Elevated risk of infection is a significant side effect of thesedrugs, of which tuberculosis (TB) is

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one of the most important [2].

According to the guidelines, Tuberculin Skin Test (TST) should be carried out before starting treatment with anti-tumor necrosis factor (TNF), but other DMARDs such as methotrexate or cyclophosphamide are not mentioned before starting the treatment. Based on available data, approved csDMARDs increase the risk of TB reactivation, but screening of latent TB is not advised for these drugs [3].

TB is a highly contagious infectious disease that spreads globally [4]. According to the World Health Organization estimate in 2016, almost a quarter of the world's population is infected with Mycobacterium tuberculosis [5]and, one and half million people worldwide lost their lives to this disease [6]. The majority of TB patients live in 22 Asian and African countries including Iran's eastern neighbors Afghanistan and Pakistan. Department of Tuberculosis and Leprosy Control of the Center for Disease Management of the Ministry of Health reported that 14.4 people per 100,000 in Iran are infected with tuberculosis every year. The incidence of tuberculosis is not evenly spread across Iran, and the prevalence is higher in the marginal regions of the country such as Sistan and Baluchestan, Khorasan, Gorgan and East Azarbaijan and Khuzestan [7].

TB infection can be reactivated during different stages and even kill the host. These processes include old age, HIV infection and use of immunosuppressive medications. Although biological and immunosuppressive medications have greatly transformed the treatment of autoimmune diseases (especially by improving symptoms), one of their important side effects is the reactivation of latent TB.

The diagnosis and treatment assessment of TB is difficult in patients taking immunosuppressive medications, and if undiagnosed and untreated, it can even lead to the patient's death [8, 9]. Therefore, before initiating some immunosuppressive medications, screening or latent or active TB is recommended [10]. Although the incidence of TB is uncommon during the treatment of patients taking immunosuppressive medications, clinicians should constantly be aware of the risk during the treatment, in spite of a negative initial screening [11]. This study aimed to evaluate the rate of positive TST in patients with a history of rheumatic disease who were treated with immunosuppressive drugs in Birjand, Iran.

Materials and Methods

The present prospective study was conducted in January and August 2020 on 40 patients with rheumatologic diseases attending the rheumatology clinic of Birjand University of Medical Sciences. In addition, 40 healthy people were selected by convenient sampling from healthy people in Birjand city, which is an endemic region for TB.

The study was conducted after obtaning the permission of the Research Ethics Committee of Birjand University of Medical Sciences (Code: IR.BUMS.REC.1398.313) and a letter of introduction from the university authorities and explaining the study objectives. The inclusion criteria for the case group were: age between 18 and 70 years, being diagnosed with a rheumatic disease, a candidate for receiving immunosuppressive medications (the diagnosis of the rheumatic disease based on diagnostic criteria and by a rheumatologist) and living in the city of Birjand. Rheumatic diseases included in this study were rheumatoid arthritis, Sjogren's syndrome, scleroderma, vasculitis, and spondyloarthritis. Immunosuppressive drugs were Anti TNF, cyclophosphamide, mycophenolate mofetil, azathioprine, prednisolone at daily doses > 10 mg and methotrexate at a dose ≥ 20 mg per week**.** The exclusion criteria were: active TB receiving anti-TB medication, Chest X-ray (CXR) patients with changes in favor of the old TB at the treatment initiation, positive TST patients at the initiation of immunosuppressive therapy, those having to terminate medication during therapy due to other side-effects, those with hepatic or renal failure, patients with acquired immune deficiency syndrome (AIDS), and those in contact with active TB patients over the past year. The inclusion criteria for the control group were: healthy people with no underlying diseases or contact with TB patients, and living within the Birjand city zone. The study objectives and method were fully explained for the participants. After obtaining written consent forms from those willing to take part, the researcher completed the questionnaire relating to demographic and disease details.

For the case group, demographic and disease-related details (medication type, dose, and duration of taking it), TST results (based on predetermined positive or negative values) and CXR (based on the presence or absence of lung involvement in favor of TB) were recorded in a researcher-made checklist. A total of 40 patients were selected according to the inclusion and exclusion criteria. The rheumatologic diseases were diagnosed according to the American College of Rheumatology (ACR) and European Alliance of Associations for Rheumatology (EULAR) criteria for each disease and by a rheumatology subspecialty based on the clinical symptoms, physical examination, and radiologic and laboratory signs. The participants' TST was controlled before treatment and at least six months afterwards. To this end, one-tenth of milliliter of purified protein derivative (PPD) solution was administered intra-dermally and read 48 to 72 hours later. Induration > 5mm was considered positive for the immunocompromised patients, ≥ 15mm for the control and healthy group, and < 5mm for all participants in both groups was negative. If the TST value was between 5 to 15 mm in the healthy control group, they were excluded from the study. CXR was also assessed in patients before therapy and at least six months afterwards. Changes in CXR in favor of latent TB included calcified and non-calcified nodules or fibrotic lesions and pleural thickening. CXR and TST were interpreted by the internal medicine PA. Given the TB endemicity of the region, the control group included 40 people from the normal population of Birjand selected according to the inclusion and exclusion criteria who were covered by the comprehensive health centers of Birjand. PPD was checked twice over six months, and induration < 5mm was taken as negative. TST was interpreted by the internal medicine PA.

Based on the data from a similar study by Paluch-Oles et al. [12], the sample size was determined 28 people per group, which was raised to 40, given a possible withdrawal of 40%. The data were analyzed in SPSS-22 using descriptive statistics to find central tendency and dispersion for the quantitative variables, qualitative data with the number (%) and Chi-squared, Fisher's exact and Mann-Whitney tests to compare the frequency of TST and changes in CXR in rheumaic patients treated with immunosuppressive medications in terms of age, gender, and duration of taking medication. Statistical significance was set at *P value* < 0.05.

Results

The present study was conducted on 40 patients with rheumatic diseases including systemic lupus erythematosus (SLE), rheumatoid arthritis, Sjogren's syndrome, scleroderma, vasculitis, and spondyloarthritis receiving immunosuppressive medications including anti-TNF, cyclophosphamide, mycophenolate mofetil, azathioprine, prednisolone at daily doses > 10 mg and methotrexate at a dose ≥ 20 mg per week. The study subjects matched in terms of age and gender (Table 1).

Table 1. Mean age and gender and Frequency distribution of TST cases in case and control groups

Group/age	**Case** **Mean ± SD**	**Control** **Mean ± SD**	***P value***
Age (years)	47.32±13.61	46.40±14.90	p=0.76*
Gender	Case Number (%)	Control Number (%)	*P value*
Male	10 (25)	12 (30)	p=0.61 **
Female	30 (75)	28 (70)	
Positive TST	3 (7.5)	0 (0)	P=0.24*
TST negative	40 (100)	37 (92.5)	

*Independent T-Test results
**fisher exact test

Fisher's exact test showed no significant difference between the two groups in terms of the frequency of positive TST cases after taking medication (*P value* = 0.56). Moreover, this test showed no significant difference across genders in terms of the frequency of positive TST (*P value* = 0.61) (Table

1). None of the subjects in the control group were TST positive. In the patients' group, it was positive in 3 people. The mean duration of the positive TST in these 3 patients was 7.6 ± 0.8 months.

No changes in CXR in favor of TB were observed in any of the case group patients before and at least six months after taking immunosuppressive medications.

In the positive TST group, 33.3% of patients had rheumatoid arthritis and 66.6% had spondyloarthritis. Also, 100% of the patients with positive TST used Cinnora (Adalimumab) and 33.3% took prednisolone and MTX (Table 2). In addition, the mean duration of using immunosuppressive medication was 14.0 ± 4.0 months in the positive TST group and 16.9 ± 12.2 months in the negative TST group, and the Mann-Whitney U test showed no significant difference between these groups (*P value* = 0.84) (Table 3).

Table 2. Frequency distribution of TST cases in terms of type of rheumatologic disease and immunosuppressive medications

TST cases/rheumatologic disease	Positive TST (n=3)	Negative TST (n=37)
Systemic lupus erythematosus (SLE)	0 (0)	10 (27.02)
Rheumatoid Arthritis	1 (33.3)	15 (40.54)
Scleroderma	0 (0)	2 (5.40)
Sjogren's syndrome	0 (0)	3 (8.10)
Vasculitis	0 (0)	1 (2.70)
spondyloarthritis *	2 (66.6)	8 (21.62)
** Immunosuppressive medication		
Cinnora (Adalimumab)***	3 (100)	11 (29.72)
Altebrel (Etanercept)	0 (0)	9 (24.32)
Remicade (infliximab)	0 (0)	1 (2.70)
Cyclophosphamide	0 (0)	4 (10.81)
Cellcept (Mycophenolate Mofetil)	0 (0)	6 (16.21)
Azathioprine	0 (0)	6 (16.21)
Prednisolone	1 (33.3)	14 (37.83)
MTX*	1 (33.3)	4 (10.81)

Number (%)
*Of those with negative TST, two patients had two concomitant rheumatologic diseases
** Some of the patients with negative TST used more than one medication
*** All three patients with positive TST used Cinnora, and as well as Cinnora, one of them used methotrexate, and another prednisolone

Table 3. Mean duration of taking immunosuppressive medication in the case group in terms of TST status

TST cases/duration of taking immunosuppressive	Positive TST (n=3) Mean ± SD	Negative TST (n=37) Mean ± SD	*P value*
Duration (months)	14.0±4.0	16.9±12.2	P=0.84*

*Mann-Whitney test results

According to the above table and the Mann-Whitney U test, no significant difference was observed between the positive TST and negative TST groups in terms of the mean duration of taking immunosuppressive medications (*P value* = 0.84).

Discussion

The results showed that 7.5% of patients with rheumatic diseases were TST positive after using immunosuppressive medications, and Fisher's exact test showed no significant difference between the case and control groups in terms of the requency of positive TST cases (P value = 0.24). No CXR changes in favor of TB was observed in any of the case group patients before and at least six months after using immunosuppressive medications.

In a study by Lee et al. [13], the activation of latent TB was assessed in 702 patients with rheumatoid arthritis, ankylosing spondylitis and Crohn's disease, treated with Anti-TNF, during which, latent TB turned into active TB in six patients. In a study by Perifanou et al. [14], 70.6% of patients with autoimmune diseases receiving immunosuppressive medications had positive TST and 22.8% had CXR changes in

favor of TB. In a study by Bonfiglioli et al., [15], patients with rheumatoid arthritis receiving anti-TNF medication for latent TB were assessed for TST and CXR, and screening for latent TB was positive in 32.6% of the patients. The present study concurs with the above studies in terms of positive TST in rheumatic patients after taking immunosuppressive medication and activation of latent TB, emphasizing the need for screening for latent TB before the initiation of these medications in rheumatologic patients. In the present study, the small number of the case group patients whose TST was positive may be due to conducting the study during the Coronavirus epidemic, when using a mask and social distancing probably reduced the incidence of respiratory infectious diseases. Paluch-Oles et al. [12],studied 81 patients with rheumatoid arthritis and nine with ankylosing spondylitis treated with Anti-TNF medications and 20 healthy people as control group. The TST test results were positive in 28.9% and the CXR changes in 5.6% in the patients group. The results of the present study are partly in line with those of the above study, indicating that using immunosuppressive medications increases the activation risk of latent TB.

The absence of CXR changes in the present study compared to similar studies can be attributed to the smaller sample size in the case group as well as the different prevalence of latent TB in the patients' place of residence. In the present study, we assessed the relative frequency of positive TST cases in terms of the type of rheumatologic disease. In the positive TST group, 33.3% of patients had rheumatoid arthritis and 66.6% had seronegative spondylo-arthritis. As in the present study, in studies conducted by Lee et al. [13], Perifanou et al. [14], Paluch-Oles et al. [12], and Cantini et al. [16], latent TB was observed in patients with spondyloarthritis after using immunosuppressive medications.

In the present study, 100% of the patients with positive TST used Cinnora (Adalimumab) and 33.3% prednisolone and MTX. In a case-report study by Mobini et al. [11], a 67-year-old female patient with rheumatoid arthritis whose initial screening for TB was negative suffered shortness of breath and exacerbation of joint symptoms while taking methotrexate and infliximab. TB was diagnosed based on the clinical findings and para-clinical assessments, such as chest CT scan and positive pleural effusion and IGRA, and medication therapy was initiated for the patient. The present study agrees with the above study in terms of TB becoming positive after taking TNF immunosuppressive medications. TB should be considered in patients treated with immunosuppressive medications at any time during the treatment.

Latent TB becomes active in some patients with rheumatologic diseases after using TNF medication as in the studies conducted by Lee et al. [13], Winthrop et al. [17], Cantini et al. [16], Soeng et al. [18], Wolfe et al. [19], and Askling et al. [20]. In Perifanou et al.'s study [14], of the medications assessed, most cases of positive TST were related to Anti-TNF. In the present study, the TST became positive in three patients after taking Cinnora. Several studies have shown that TB manifestations and diagnosis are difficult in patients taking immunosuppressive medications including TNF, and TB is rather extra-pulmonary and in unusual sites, and it is rarely diagnosed and may even cause death [8, 9, 21]. In addition, by discontinuing these medications and initiating anti-TB therapy, the patient may develop immune reconstitution inflammatory syndrome (IRIS), which can be extremely risky [22]. The mean duration of taking immunosuppressive medication was 14.0 ± 4.0 months in the positive TST group and 16.9 ± 12.2 months in the TST negative, with no significant difference between the two groups according to the Mann-Whitney U test (*P value* = 0.84).

According to many studies, the interval between the initiation of TNF medications and the onset of TB symptoms and TB infection is different [10, 23]. Given that the interval between the onset of TB symptoms and initiation of TNF can be stretched from three months to even several years [10], repeating TST a year after the initiation of treatment is recommended if the TST is negative [24].

A meta-analytical study conducted by Ai et al. [25] showed that the relative risk of TB in patients with rheumatoid arthritis taking TNF medications is 4.03, and the preventive treatment 65%.

In the present study, no CXR change in favor of TB was observed in the case group before and at

least of latent TB in these patients reduces the risk of developing TB by six months after using immunosuppressive medications. In Perifanou et al.'s study [14], CXR changes in favor of TB were observed in 22.8% of rheumatologic patients taking immunosuppressive medications, and in Paluch-Oles et al.'s [12] study, these changes were found in 5.5% of such patients, which disagrees with the present study results. This disagreement could be due to the difference in the duration of using immunosuppressive medications, regional endemicity in terms of TB, and the presence of other pulmonary diseases.

There were some limitations in the current study including the negative TST due to the use of glucocorticoids and other immuno-suppressive drugs and small sample size. Therefore, it is recommended that patients who are at higher risk for tuberculosis activation have an IGRA test every 6 months or annually.

Conclusion

The results showed that the activation of latent TB is possible in patients using immunosuppressive medications, particularly Anti-TNF, and in TB endemic regions, clinicians should be aware of the risk at any time after initiating treatment with such medications even after negative initial screening tests, and monitor the patients regularly.

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Conflict of interest

The authors declare no conflict of interest.

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References

1. Au K, Reed G, Curtis JR, Kremer JM, Greenberg JD, Strand V. *et al*. High disease activity is associated with an increased risk of infection in patients with rheumatoid arthritis. ***Ann Rheum Dis*** 2011; 70(5):785-91. doi: 10.1136/ard.2010.128637.
2. Arkema EV, Jonsson J, Baecklund E, Bruchfeld J, Feltelius N, Askling J. 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):1212-17. doi: 10.1136/annrheumdis-2013-204960.
3. Chiu Y-M, Chen D-Y. Infection risk in patients undergoing treatment for inflammatory arthritis: non-biologics versus biologics. ***Expert Rev Clin Immunol*** 2020; 16(2):207-28. doi: 10.1080/ 1744666X. 2019. 1705785.
4. Berju A, Haile B, Nigatu S, Mengistu A, Birhan G. Smear-Positive Tuberculosis Prevalence and Associated Factors among Pregnant Women Attending Antinatal Care in North Gondar Zone Hospitals, Ethiopia. ***Int J Microbiol*** 2019; 2019:9432469. doi: 10.1155/2019/9432469.
5. Cohen A, Mathiasen VD, Schön T, Wejse C. The global prevalence of latent tuberculosis: a systematic review and meta-analysis. ***Eur Respir J*** 2019; 54(3):1900655. doi: 10.1183/13993003.00655-2019.
6. Global status report on alcohol and health 2018. [https://www.who.int/publications/i/item/9789241565639].
7. Daneshi S, Ebadifard Azar F, Ahmadi Tabatabaei SV, Alian Samakkhah S, Kamali A, Hushmandi K. *et al*. Incidence Rate and Epidemiological Status of Tuberculosis in Kerman City in 2018. ***J Mar Med*** 2021; 2(4):210-15. doi:10.30491/2.4.210
8. Bielewicz-Zielińska A, Brzezicki J, Rymko M, Jeka S. Unusual location of tuberculosis in the course of tumor necrosis factor α inhibitor therapy. ***Reumatologia*** 2015; 53(3):161-64. doi: 10.5114/reum.2015.53139.
9. Garcia-Lopez A, Burgueno-Montanes C. Importance of tuberculosis screening before inhibiting tumour necrosis factor-alpha therapy. ***Arch Soc Esp Oftalmol*** 2013; 88(1):36-39. doi: 10.1016/j.oftal.2011.10.006.
10. Bernal JA, Andrés M, Jovaní V, Sevila RG, Begazo A, Vela P. Primary tuberculosis infection in patients treated with tumor necrosis factor-alpha antagonists and a negative initial screening. ***Reumatol Clín*** 2016; 12(2):81-84. doi: 10.1016/j.reuma.2015.04.001.
11. Mobini M, Niksolat F, Ghasemian R, Sharifpour A, Valipour S. De novo tuberculosis during anti-tumor necrosis factor-alpha therapy in a rheumatoid arthritis patient with negative initial screening. ***J Mazandaran Univ Med Sci*** 2017; 26(144):382-88.
12. Paluch-Oleś J, Magryś A, Kozioł-Montewka M, Koszarny A, Majdan M. Identification of latent tuberculosis infection in rheumatic patients under consideration for treatment with anti-TNF-α vagents.

Arch Med Sci 2013; 9(1):112-17. doi: 10.5114/aoms.2013.33352.

13. Lee EH, Kang YA, Leem AY, Park MS, Kim YS, Kim SK. *et al*. Active tuberculosis incidence and characteristics in patients treated with tumor necrosis factor antagonists according to latent tuberculosis infection. ***Sci Rep*** 2017; 7(1):6473. doi: 10.1038/s41598-017-06899-1.
14. Perifanou D, Zoe D, Petinaki E, Konstantinou K, Gourgoulianis K. Screening for Latent Tuberculosis Infection in Patients with Autoimmune Diseases Before Initiating TNF-α Inhibitors Therapy. ***Mater Sociomed*** 2018; 30(1):32-37. doi: 10.5455/msm.2018.30.32-37.
15. Bonfiglioli K, Ribeiro A, Moraes J, Saad C, Souza F, Calich A. *et al*. LTBI screening in rheumatoid arthritis patients prior to anti-TNF treatment in an endemic area. ***Int J Tuberc Lung Dis*** 2014; 18(8):905-11. doi: 10.5588/ijtld.13.0755.
16. Cantini F, Nannini C, Niccoli L, Iannone F, Delogu G, Garlaschi G. *et al*. Guidance for the management of patients with latent tuberculosis infection requiring biologic therapy in rheumatology and dermatology clinical practice. ***Autoimmun Rev*** 2015; 14(6):503-09. doi: 10.1016/j.autrev.2015.01.011.
17. Winthrop KL. Risk and prevention of tuberculosis and other serious opportunistic infections associated with the inhibition of tumor necrosis factor. ***Nat Clin Pract Rheumatol*** 2006; 2(11):602-10. doi: 10.1038/ncprheum0336.
18. Seong S-S, Choi C-B, Woo J-H, Bae KW, Joung C-L, Uhm W-S. *et al*. Incidence of tuberculosis in Korean patients with rheumatoid arthritis (RA): effects of RA itself and of tumor necrosis factor blockers. ***J Rheumatol*** 2007; 34(4):706-11.
19. Wolfe F, Michaud K, Anderson J, Urbansky K. Tuberculosis infection in patients with rheumatoid arthritis and the effect of infliximab therapy. ***Arthritis Rheum*** 2004; 50(2):372-79. doi: 10.1002/art.20009.
20. Askling J, Fored CM, Brandt L, Baecklund E, Bertilsson L, Cöster 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):1986-92. doi: 10.1002/art.21137.
21. Kisacik B, Pamuk ON, Onat AM, Erer SB, Hatemi G, Ozguler Y. *et al*. Characteristics predicting tuberculosis risk under tumor necrosis factor-α inhibitors: report from a large multicenter cohort with high background prevalence. ***J rheumatol*** 2016; 43(3):524-29. doi: 10.3899/jrheum.150177.
22. Manea E, Munteanu D, Jipa R, Moroti R, Arama V, Diaconu I-A. *et al*. Immune reconstitution inflammatory syndrome in central nervous system tuberculosis. ***Pneumologia*** 2015; 64(4):32-36.
23. Guinard E, Bulai Livideanu C, Barthélémy H, Viguier M, Reguiai Z, Richard M. *et al*. Active tuberculosis in psoriasis patients treated with TNF antagonists: a French nationwide retrospective study. ***J Eur Acad Dermatol Venereol*** 2016; 30(8):1336-41. doi: 10.1111/jdv.13633.
24. Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM. *et al*. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. ***Arthritis Care Res (Hoboken)*** 2012; 64(5):625-39. doi: 10.1002/acr.21641.
25. Ai J-W, Zhang S, Ruan Q-L, Yu Y-Q, Zhang B-Y, Liu Q-H. *et al*. The risk of tuberculosis in patients with rheumatoid arthritis treated with tumor necrosis factor-α antagonist: a metaanalysis of both randomized controlled trials and registry/cohort studies. ***J Rheumatol*** 2015; 42(12):2229-37. doi: 10.3899/jrheum.150057.