Archives of the Balkan Medical Union
vol. 53, no. 1, pp. 89-95
March 2018

REVIEW

PULMONARY INVOLVEMENT IN RHEUMATOID ARTHRITIS – ANOTHER FACE OF THE COIN

Georgiana Iftimie[1], Ovidiu G. Bratu[2,3], Bogdan Socea[2,4], Mihaela A. Iancu[2], Ana Maria A. Stănescu[2], Giorgiana Dediu[5], Bianca Paraschiv[6], Camelia Diaconu[1,2]

[1] Clinical Emergency Hospital of Bucharest, Bucharest, Romania
[2] „Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[3] Emergency Universitary Central Military Hospital, Bucharest, Romania
[4] Emergency Clinical Hospital "Sfântul Pantelimon", Bucharest, Romania
[5] Clinical Emergency Hospital „Sf. Ioan", Bucharest, Romania
[6] „Sf. Stefan" Hospital, Bucharest, Romania

Abstract

Rheumatoid arthritis (RA) is a systemic autoimmune disorder that causes progressive, symmetric, erosive destruction of cartilage and bone, which is usually associated with autoantibodies production. It is common that articular signs and symptoms develop long before extraarticular signs, but sometimes lung involvement is the first manifestation of RA and the most aggressive feature of the disease. Respiratory symptoms can precede the articular symptoms in 10–20% of cases. However, they may be masked by the poor functional status from joint disease or chronic inflammation. The pulmonary involvement can be due to the chronic inflammation caused by the disease or it can be secondary to immune-modulating medication. The pulmonary disease due to the disease itself includes: interstitial lung diseases, airways involvement (large and small airways), pleural involvement, rheumatoid pulmonary nodules and vascular pathology. The most used medication in patients with RA, such as metotrexate, leflunomide, TNF alpha blockers, but also other used drugs, may cause pulmonary diseases.

Résumé

Implication pulmonaire induite par le traitement de la polyarthrite rhumatoïde –le revers de la monnaie

La polyarthrite rhumatoïde (PR) est une maladie auto-immune systémique qui provoque une destruction progressive, symétrique et érosive du cartilage et des os, généralement associée à la production d'anticorps. Il est fréquent que les signes et symptômes articulaires se développent longtemps avant les signes extra-articulaires, mais parfois la maladie pulmonaire peut être la première manifestation de la PR et la caractéristique la plus agressive. Les symptômes respiratoires peuvent précéder les symptômes articulaires dans 10 à 20% des cas. Cependant, ils peuvent être masqués par le mauvais état fonctionnel induit par la maladie articulaire ou l'inflammation chronique. L'atteinte pulmonaire peut être due à l'inflammation chronique causée par la maladie ou peut être secondaire à un médicament immunomodulateur. La maladie pulmonaire elle-même comprend maladies pulmonaires interstitielles, atteinte des voies aériennes (grandes et petites voies respiratoires), atteinte pleurale, nodules pulmonaires

Corresponding author: Camelia Diaconu
Internal Medicine Clinic, Clinical Emergency Hospital of Bucharest
8 Calea Floreasca, Bucharest, Romania
e-mail: drcameliadiaconu@gmail.com

Key words: rheumatoid arthritis, pulmonary involvement, interstitial lung disease, drug toxicity.

rhumatoïdes et pathologie vasculaire. Les médicaments les plus utilisés chez les patients atteints de PR, tels que le méthotrexate, le léflunomide, les alpha-bloquants TNF, mais aussi d'autres médicaments utilises, peuvent provoquer des maladies pulmonaires.

Mots-clés: polyarthrite rhumatoïde, atteinte pulmonaire, pneumopathie interstitielle, toxicité médicamenteuse.

Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disorder that causes progressive, symmetric, erosive destruction of cartilage and bone, which is usually associated with autoantibodies production. Chronic inflammation causes thickening of the synovium, resulting in swelling and pain in and around the joints.

If inflammation continues, it can damage the cartilage, elastic tissue that covers the ends of bones in a joint, as well as the bones themselves. Over time, a loss of cartilage appears, and the joint space between bones can become smaller. Joints become loose, unstable, painful, lose their mobility and deformity can also occur. Joint damage is irreversible, and because it occurs early, early diagnosis and aggressive treatment of RA are recommended.

The incidence of RA is about 1% in developed countries, affecting mostly women[1]. The lung is a common site of extra-articular disease and is an important contributor to mortality and morbidity[2].

Types of pulmonary involvement

It is common that articular signs and symptoms develop long before extra-articular disease, but sometimes lung involvement is the first manifestation of RA and the most aggressive feature of the disease. Respiratory symptoms may precede the articular symptoms in 10–20% of cases[3]. However, they may be masked by the poor functional status from joint disease or chronic inflammation.

The pulmonary involvement can be induced by the chronic inflammation which characterizes the disease or can be secondary to immune-modulating medication.

Interstitial lung disease (ILD)

It is a type of specific disorder that includes different parenchymal lung disorders classified by distinct clinical, pathologic, and radiographic features. Although all the ILD group disorders have been reported in RA, it seems that usual interstitial pneumonia (UIP) and nonspecific interstitial pneumonia (NSIP) are the most common forms associated with RA.

A strong connection between male gender, typically in the fifth to sixth decade of life, smoking history (one study finding an odds ratio of 3.8 for those who smoked >25 pack-years) and ILD associated with RA has been described[4]. The circulating immune complexes, as well as high levels of rheumatoid factor, are incriminated in all extra-articular manifestations, including ILD.

Pathogenesis of ILD. The basic mechanism of developing ILD in patients with RA is not clearly understood yet. Genetic factors, like HLA-B54, HLA-B40, and HLA-DR4, have been incriminated. This seems to be the case especially in individuals

Table 1. Pulmonary disease induced by rheumatoid arthritis.

Parenchymal
Interstitial lung disease (i.e. usual interstitial pneumonia, nonspecific interstitial pneumonia, acute interstitial pneumonia/diffuse alveolar damage and organizing pneumonia)
Pleural disease
Pleural effusion
Pneumothorax
Bronchopleural fistula
Trapped lung syndrome
Airway obstruction
Cricoarytenoid arthritis
Bronchiectasis
Follicular bronchiolitis
Obliterative (constrictive) bronchiolitis
Nodules
Rheumatoid nodules
Caplan syndrome
Vascular disease
Rheumatoid vasculitis
Pulmonary hypertension
Other
Drug toxicity
Infection
Malignancy
Thoracic cage restriction
Thromboembolic disease

who have the shared epitope human leukocyte antigen (HLA)-DRB1. A large case-control study from Sweden demonstrated a 21-fold increased risk of developing RA among anti-CCP positive patients, smokers, with two copies of the shared epitope gene, versus non-smokers who did not have the shared epitope gene[5]. Similarly, cigarette smoking has been linked with both RA and RA-ILD[6,7]. Some authors speculate that lungs may be a site of initial immune dysregulation that leads to the development of RA[8]. Citrullinated proteins have been identified in bronchoalveolar lavage fluid from cigarette smokers without RA, and RA-related autoantibodies are detectable in the sputum of patients identified to be at risk for RA[9,10].

Clinical symptoms. Dyspnea, cough, fatigue or general weakness have been frequently reported in patients with RA. Symptoms usually progress over time; however, the rate of progression is variable from patient to patient and between the different histopathologic forms of ILD. Studies indicate that patients with UIP may progress faster than other subtypes of ILD in RA and at rates similar to those reported for idiopathic pulmonary fibrosis (IPF)[11,12].

Radiography. The most common feature is UIP pattern, characterized by peripheral basilar predominant reticular abnormalities, honeycombing, traction bronchiectasis, and minimal ground-glass opacification. NSIP is the other common pattern in RA-ILD and is characterized by reticulation and ground-glass, with little or no architectural distortion or honeycombing[13].

Airways involvement

Prevalence of airways disease in RA is high; it occurs in 39% to 60% of patients[14-16]. Any part of the airway may be involved, including the large airways (upper and lower) and distal small airways. Cricoarytenoid arthritis and bronchiectasis are the most common forms of large airway involvement, although few patients have clinically significant symptoms[17]. Bronchiectasis, defined as destruction and widening of the large airways, occurs in 16% to 58% of patients with RA[18,19]. Most cases are not clinically significant but, when present, symptoms include cough and sputum production.

Small airways disease involves the distal airways (2 mm in diameter or less). Two forms of small airways disease (follicular bronchiolitis and constrictive bronchiolitis) have been described in association with RA. Follicular bronchiolitis is identified at histopathology by the presence of hyperplastic lymphoid follicles with reactive germ cell centers within bronchiole walls. Constrictive bronchiolitis (also referred to as obliterative bronchiolitis) is identified by concentric narrowing of membranous and respiratory bronchioles caused by peribronchiolar inflammation and fibrosis, without evidence of lymphoid hyperplasia[20]. Prognosis is poor; however, in a recent prospective study, in connective tissue disease (CTD)-associated bronchiolitis (in which 50% of patients had RA), the forced expiratory volume in 1 second showed stability over time in both forms, suggesting that bronchiolitis associated with CTD may have a less aggressive course than idiopathic disease[21,22].

When bronchiectasis are severe enough to produce clinical symptoms, they may complicate the use of immunosuppressive medications, particularly anti-TNF agents, as both bronchiectasis and anti-TNF therapy increase the risk of pulmonary infections. Among patients with RA and bronchiectasis, mortality rates are higher than for either condition alone [23].

Pleural involvement

Pleuritis and pleural effusions are often found in RA. About 3–5% of patients are symptomatic [24,25]. The pleural disease can precede joint disease and is more common in older males and those with rheumatoid nodules. RA effusions are exudative and sterile, unilateral, but bilateral effusion may appear, too, often with low glucose and low pH[26]. Pathognomonic for rheumatoid effusions are macrophages and multinucleate giant cells, together with granulomatous debris[27]. These findings mirror those in rheumatoid synovitis or rheumatoid nodules. Fever and pleuritic chest pain are common, but cough is absent unless there is comorbid parenchymal lung disease.

Rheumatoid pulmonary nodules

They usually appear in patients with longstanding disease and subcutaneous nodules. Nodules may be single or multiple, measuring from a few millimeters to several centimeters. Rheumatoid nodules are pulmonary lesions histologically composed of a central fibrinoid necrotic region surrounded by mononuclear cells, granulation tissue, lymphocytes, plasma cells, and fibroblasts. They are typically found in pleural or subpleural regions, occasionally with cavitation[28,29]. Nodules are asymptomatic unless they cavitate or rupture, in which case infection, pleural effusion or bronchopleural fistula may occur. Uncomplicated nodules may spontaneously regress or improve with standard rheumatoid arthritis therapy. However, rheumatoid nodules have, at times, been noted to paradoxically enlarge with rheumatoid arthritis treatment. In particular, this has been observed with methotrexate treatment[30].

Vascular disease

Pulmonary arterial hypertension is rare in RA. The most common form of vascular involvement in

RA is rheumatoid vasculitis, which is characterized pathologically by the presence of a destructive inflammatory infiltrate within small and medium-sized blood vessel walls. A large study that involved 146 patients with RA has found that 21% of patients had mild-to-moderate pulmonary hypertension on echocardiography, in the absence of clinically significant heart or lung disease[30]. None of the patients with pulmonary hypertension were symptomatic[31]. Patients with RA are also at increased risk of venous thromboembolism, both deep venous thrombosis and pulmonary thromboembolism, compared to those without RA[32,33]. Patients with RA and more severe extra-articular disease are at even greater risk of venous thromboembolism, supporting the hypothesis that some of the increase in risk is attributable to prothrombotic effects of chronic inflammation[34,35].

Drug toxicity

The first preferred therapy for RA is a disease-modifying or immunosuppressant treatment to influence the articular symptoms. This medication is used to lower and balance the inflammatory cytokine level, but it has some side effects, including pulmonary involvement. It is difficult to show the real causality, as patients with RA are prone to lung complications from infection, other medications and the disease itself.

Methotrexate

Methotrexate is usually the first-line immunomodulator drug used to treat articular manifestations and to prevent joint destruction. It has been associated with pulmonary disease since the first study in 1983 and a lot of cases have been reported ever since[36]. The first year of treatment and the higher dose of methotrexate are more likely linked to pneumonitis reactions.

Symptoms include dyspnea and nonproductive cough, with or without systemic symptoms. Imaging findings are relatively nonspecific, with diffuse pulmonary opacities or patchy consolidation seen on chest radiographs and computed tomography scans. Chest X-rays may be normal in the early stages of the disease. Broncho-alveolar lavage (BAL) and lung biopsy are more helpful in ruling out alternative causes (i.e. infection) than in establishing the diagnosis of methotrexate-induced lung injury, although the presence of poorly formed non-necrotizing granulomas and scattered eosinophils may suggest methotrexate-induced hypersensitivity pneumonitis, as these are not typical findings in RA-ILD[36-38].

A recent meta-analysis of 22 studies involving patients with RA treated with methotrexate (n=4544) versus other agents (including disease modifying anti-rheumatic drugs and biological agents) found a small increase in the risk of respiratory infections (RR 1.11, 95% CI 1.02–1.21), but not in noninfectious complications, such as pneumonitis, or death from pulmonary causes among those treated with methotrexate [39].

A small case-control study from Australia found that patients who developed pneumonitis were more likely to have had pre-existing lung disease and shorter duration of therapy, although neither trend reached statistical significance[40].

Genetic predisposition to drug sensitivity may play a role as well. A recent case-control study of Japanese patients with RA, treated with methotrexate, found a significant association between the development of pneumonitis and the presence of the HLA-A*31:01 allele[41].

It seems that methotrexate is associated with a high number of rheumatoid nodules in the lungs, but cigarette smoking has not been shown to be a risk factor for the development of methotrexate-associated pulmonary toxicity.

Methotrexate has not been shown to accelerate the progression of underlying RA-ILD, but the increased risk of pneumonitis means that it may not always be the safest first-line disease-modifying anti-rheumatic drug (DMARD) in such patients.

Leflunomide

It is another important drug used to treat RA articular signs and symptoms, usually as second-line therapy for those who fail or have methotrexate contraindications. Leflunomide has also been reported to cause pneumonitis, although this appears to occur especially in Japanese and Korean patients[42]. It has been associated with the development and or exacerbation of ILD, potentially secondary to an active metabolite that may induce transition of lung epithelial cells to myofibroblasts, a process known as the epithelial-mesenchymal transition[43].

It is important to note that in at least one of these studies, all patients treated with leflunomide had been previously exposed to methotrexate, which may have been a confounding factor[44].

TNF-alpha inhibitors

There are reports that TNF agents used in the treatment of RA may accelerate the progression of ILD and patients can develop pulmonary fibrosis. Reports of new-onset ILD have been described for all five TNF-α inhibitors currently approved for the treatment of rheumatoid arthritis[45,46]. Studies have reported sarcoid-like granulomatous disease, organizing pneumonia and exacerbation of existing pulmonary affection.

Because methotrexate was co-prescribed, it is unclear how many of these cases were real, although most of the cases occurred within 3 months after starting anti-TNF therapy, with a high mortality.

A report from the British Society for Rheumatology Biologics Register (BSRBR) has shown that mortality was not greater in 299 patients with RA-ILD treated with anti-TNF therapy than in those 68 treated with DMARDs alone. It has been suggested that patients with prior RA-ILD should receive anti-TNF treatment with caution[47].

A study included 122 cases of new-onset or exacerbated ILD, treated with TNF-α inhibitors[48]. 63% of these patients had been treated with methotrexate, and 38% had pre-existing ILD[49]. 15 (29%) patients who died were aged >65 years and had prior ILD, with longer duration of ILD being associated with risk of death[48]. In contrast, a large cohort study of 8417 patients with autoimmune disease did not show any significant difference in the incidence of ILD between those who were treated with anti-TNF therapy (0.5%) and those were treated with other therapies (0.3%)[49].

Other drugs

Another type of medication, more rarely used in the treatment of RA, can also cause pulmonary side effects.

Rituximab, used for the treatment of lymphoma, is now also used for the treatment of RA. Pulmonary toxicity has rarely been reported in patients treated with rituximab, and is calculated to occur in <0.03% of 540 000 treated cases[50]. There have been reports of organizing pneumonia associated with rituximab in rheumatoid arthritis[51].

A randomized controlled trial evaluating the efficacy and safety of rituximab in 465 patients with rheumatoid arthritis did not note any correlation with ILD[52]. In fact, small case studies have suggested a beneficial effect of rituximab on connective tissue disease-associated ILD[53].

Non-steroidal anti-inflammatory drugs seem to be connected to the risk of developing organizing pneumonitis.

Sulfasalazine and penicillamine have been associated with obliterative bronchiolitis and eosinophilic pneumonia.

Azathioprine and tacrolimus have been reported to exacerbate pre-existing ILD[54]. Anti-IL6 agent tocilizumab[55,56] has reports of exacerbations of pre-existing ILD[57,58] and developing of noninfectious pneumonia.

Abatacept, an inhibitor of T-cell co-stimulation that binds B7 (CD80 and CD86) on antigen presenting cells, has been associated with chronic obstructive pulmonary disease exacerbations, but there has been only one report of possible ILD exacerbation described in the literature[59]. It is difficult to quantify the pulmonary toxicity of each drug if they are used in combination.

Conclusions

RA is a chronic disease that may be associated with pulmonary involvement, either due to the disease itself, or to the side effects of the treatment. In some patients, the respiratory symptoms and signs may precede the articular clinical manifestations specific to the disease. The pulmonary side effects of drugs used for the treatment of RA should be carefully monitored, as they impair the quality of life of these patients and may lead to serious complications.

Compliance with Ethics Requirements:

„The authors declare no conflict of interest regarding this article"

„The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law."

References

1. Gibofsky A. Overview of epidemiology, pathophysiology, and diagnosis of rheumatoid arthritis. *Am J Manag Care* 2012;18:S295-302.
2. Lee HK, Kim DS, Yoo B, et al. Histopathologic pattern and clinical features of rheumatoid arthritis-associated interstitial lung disease. *Chest.* 2005; 127(6):2019–27.
3. O'Dwyer DN, Armstrong ME, Cooke G, et al. Rheumatoid arthritis associated interstitial lung disease. *Eur J Intern Med* 2013; 24: 597–603.
4. Saag KG, Cerhan JR, Kolluri S, et al. Cigarette smoking and rheumatoid arthritis severity. *Ann Rheum Dis* 1997;56: 463–469.
5. Klareskog L, Stolt P, Lundberg K, et al. A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination.*Arthritis Rheum* 2006; 54: 38–46.
6. Gochuico BR, Avila NA, Chow CK, et al. Progressive preclinical interstitial lung disease in rheumatoid arthritis. *Arch Intern Med.* 2008; 168(2):159–66.
7. Albano SA, Santana-Sahagun E, Weisman MH. Cigarette smoking and rheumatoid arthritis. *Semin Arthritis Rheum.* 2001; 31(3):146–59.
8. Demoruelle MK, Deane KD, Holers VM. When and where does inflammation begin in rheumatoid arthritis? *Curr Opin Rheumatol.* 2014; 26(1):64–71.
9. Makrygiannakis D, Hermansson M, Ulfgren AK, et al. Smoking increases peptidylarginine deiminase 2 enzyme expression in human lungs and increases citrullination in BAL cells. *Ann Rheum Dis.* 2008; 67(10):1488–92.

10. Willis VC, Demoruelle MK, Derber LA, et al. Sputum autoantibodies in patients with established rheumatoid arthritis and subjects at risk of future clinically apparent disease. *Arthritis Rheum.* 2013; 65(10):2545–54.
11. Kim EJ, Elicker BM, Maldonado F, et al. Usual interstitial pneumonia in rheumatoid arthritis-associated interstitial lung disease. *Eur Respir J.* 2010; 35(6):1322–8.
12. Park JH, Kim DS, Park IN, et al. Prognosis of fibrotic interstitial pneumonia: idiopathic versus collagen vascular disease-related subtypes. *Am J Respir Crit Care Med.* 2007; 175(7):705–11.
13. Dawson JK, Fewins HE, Desmond J, et al. Fibrosing alveolitis in patients with rheumatoid arthritis as assessed by high resolution computed tomography, chest radiography, and pulmonary function tests. *Thorax.* 2001; 56(8):622–7.
14. Geddes DM, Webley M, Emerson PA. Airways obstruction in rheumatoid arthritis. *Ann Rheum Dis.* 1979; 38(3):222–5.
15. Collins RL, Turner RA, Johnson AM, et al. Obstructive pulmonary disease in rheumatoid arthritis. *Arthritis Rheum.* 1976; 19(3):623–8.
16. Hassan WU, Keaney NP, Holland CD, et al. Bronchial reactivity and airflow obstruction in rheumatoid arthritis. *Ann Rheum Dis.* 1994; 53(8):511–4.
17. Brazeau-Lamontagne L, Charlin B, Levesque RY, et al. Cricoarytenoiditis: CT assessment in rheumatoid arthritis. Radiology. 1986; 158(2):463–6. [PubMed: 3941873]
18. Metafratzi ZM, Georgiadis AN, Ioannidou CV, et al. Pulmonary involvement in patients with early rheumatoid arthritis. *Scand J Rheumatol.* 2007; 36(5):338–44.
19. Kochbati S, Boussema F, Ben Miled M, et al. Bronchiectasis in rheumatoid arthritis. High resolution computed pulmonary tomography. *Tunis Med.* 2003; 81(10):768–73.
20. Pipavath SJ, Lynch DA, Cool C, et al. Radiologic and pathologic features of bronchiolitis. *AJR Am J Roentgenol.* 2005; 185(2):354–63.
21. Fernandez Perez ER, Krishnamoorthy M, Brown KK, et al. FEV1 over time in patients with connective tissue disease-related bronchiolitis. *Respir Med.* 2013; 107(6):883–9.
22. Devouassoux G, Cottin V, Liote H, et al. Characterisation of severe obliterative bronchiolitis in rheumatoid arthritis. *Eur Respir J.* 2009; 33(5):1053–61.
23. Wilczynska MM, Condliffe AM, McKeon DJ. Coexistence of bronchiectasis and rheumatoid arthritis: revisited.*Respir Care* 2013; 58: 8.
24. Balbir-Gurman A, Yigla M, Nahir AM, et al. Rheumatoid pleural effusion. *Semin Arthritis Rheum* 2006; 35:368–378.
25. Corcoran JP, Ahmad M, Mukherjee R, et al. Pleuro-pulmonary complications of rheumatoid arthritis. *RespirCare* 2014; 59: e55–e59.
26. Avnon LS, Abu-Shakra M, Flusser D, et al. Pleural effusion associated with rheumatoid arthritis: what cell predominance to anticipate? *Rheumatol Int.* 2007; 27(10):919–25.
27. Naylor B. The pathognomonic cytologic picture of rheumatoid pleuritis. The 1989 Maurice Goldblatt Cytology award lecture. *Acta Cytol.* 1990; 34(4):465–73.
28. Anaya JM, Diethelm L, Ortiz LA, et al. Pulmonary involvement in rheumatoid arthritis. *Semin Arthritis Rheum.* 1995; 24(4):242–54.
29. Walters MN, Ojeda VJ. Pleuropulmonary necrobiotic rheumatoid nodules. A review and clinicopathological study of six patients. *Med J Aust.* 1986; 144(12):648–51.
30. Combe B, Didry C, Gutierrez M, et al. Accelerated nodulosis and systemic manifestations during methotrexate therapy for rheumatoid arthritis. *Eur J Med* 1993; 2: 153–156.
31. Dawson JK, Goodson NG, et al. Raised pulmonary artery pressures measured with Doppler echocardiography in rheumatoid arthritis patients. Rheumatology (Oxford) 2000; 39: 1320–1325.
32. Chung WS, Peng CL, Lin CL, et al. Rheumatoid arthritis increases the risk of deep venous thrombosis and pulmonary thromboembolism: a nationwide cohort study. *Ann Rheum Dis* 2014; 73: 7.
33. Bacani AK, Gabriel SE, Crowson CS, et al. Noncardiac vascular disease in rheumatoid arthritis: increase invenous thromboembolic events? *Arthritis Rheum* 2012; 64: 9.
34. Van den Oever IA, Sattar N, Nurmohamed MT. Thromboembolic and cardiovascular disease in rheumatoid arthritis: role of the haemostatic system. *Ann Rheum Dis* 2014; 73: 954–957.
35. Liang KP, Liang KV, Matteson EL, et al. Incidence of noncardiac vascular disease in rheumatoid arthritis and relationship to extraarticular disease manifestations. *Arthritis Rheum* 2006; 54: 642–648.
36. Roubille C, Haraoui B. Interstitial lung diseases induced or exacerbated by DMARDS and biologic agents in rheumatoid arthritis: a systematic literature review. *Semin Arthritis Rheum* 2014; 43: 613–626.
37. Saravanan V, Kelly C. Drug-related pulmonary problems in patients with rheumatoid arthritis. Rheumatology(Oxford) 2006; 45: 787–789.
38. Barrera P, Laan RF, van Riel PL, et al. Methotrexate-related pulmonary complications in rheumatoid arthritis. *Ann Rheum Dis* 1994; 53: 434–439.
39. Conway R, Low C, Coughlan RJ, et al. Methotrexate and lung disease in rheumatoid arthritis – a meta-analysis of randomized controlled trials. *Arthritis Rheum* 2014; 66: 803–812.
40. Carroll GJ, Thomas R, Phatouros CC, et al. Incidence, prevalence and possible risk factors for pneumonitis in patients with rheumatoid arthritis receiving metotrexate. *J Rheumatol* 1994; 21:51-54
41. Furukawa H, Oka S, Shimada K, et al. HLA-A*31:01 and methotrexate-induced interstitial lung disease in Japanese rheumatoid arthritis patients: a multidrug hypersensitivity marker? *Ann Rheum Dis* 2013; 72: 153–155.
42. Kamata Y, Nara H, Kamimura T et al. Rheumatoid arthritis complicated with acuteinterstitial pneumonia induced by leflunomide as an adverse reaction. *Intern Med* 2004;43(12):1201-4.
43. Namba T, Tanaka KI, Ito Y, et al. Induction of EMT-like phenotypes by an active metabolite of leflunomide and its contribution to pulmonary fibrosis. *Cell Death Differ* 2010; 17: 1882–1895.
44. Ju JH, Kim SI, Lee JH, et al. Risk of interstitial lung disease associated with leflunomide treatment in Korean patients with rheumatoid arthritis. *Arthritis Rheum* 2007; 56: 2094–2096.
45. Hadjinicolaou AV, Nisar MK, Bhagat S, et al. Non-infectious pulmonary complications of newer biological agents for rheumatic diseases – a systematic literature review. *Rheumatology* (Oxford) 2011; 50: 2297–2305.
46. Lager J, Hilberg O, Løkke A, et al. Severe interstitial lung disease following treatment with certolizumab pegol: a case report. *Eur Respir Rev* 2013; 22: 414–416.
47. Chen JJ, Branstetter BF, Myers EN. Cricoarytenoid rheumatoid arthritis: an important consideration in aggressive lesions of the larynx. *AJNR Am J Neuroradiol* 2005; 26: 970–972.

48. Perez-Alvarez R, Perez-de-Lis M, Diaz-Lagares C, et al. Interstitial lung disease induced or exacerbated by TNF-targeted therapies: analysis of 122 cases. *Semin Arthritis Rheum* 2011; 41: 256–264.
49. Herrinton LJ, Harrold LR, Liu L, et al. Association between anti-TNF-α therapy and interstitial lung disease. *Pharmacoepidemiol Drug Saf* 2013; 22: 394–402.
50. Kimby E. Tolerability and safety of rituximab (MabThera). *Cancer Treat Rev* 2005; 31: 456–473.
51. Soubrier M, Jeannin G, Kemeny JL, et al. Organizing pneumonia after rituximab therapy: two cases. *Joint Bone Spine* 2008; 75: 362–365.
52. Emery P, Fleischmann R, Filipowicz-Sosnowska A, et al. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phase IIB randomized, double-blind,placebo-controlled, dose-ranging trial. *Arthritis Rheum* 2006; 54: 1390–1400.
53. Keir GJ, Maher TM, Ming D, et al. Rituximab in severe, treatment-refractory interstitial lung disease. *Respirology* 2014; 19: 353–359.
54. Hallowell RW, Horton MR. Interstitial lung disease in patients with rheumatoid arthritis: spontaneous and drug induced. *Drugs* 2014; 74: 443–450.
55. Smolen JS, Beaulieu A, Rubbert-Roth A, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. *Lancet* 2008; 371: 987–997.
56. Nishimoto N, Yoshizaki K, Miyasaka N, et al. Treatment of rheumatoid arthritis with humanized anti-interleukin-6 receptor antibody: a multicenter, double-blind, placebo-controlled trial. *Arthritis Rheum* 2004;50: 1761–1769.
57. Kawashiri SY, Kawakami A, Sakamoto N, et al. A fatal case of acute exacerbation of interstitial lung disease in a patient with rheumatoid arthritis during treatment with tocilizumab. *Rheumatol Int* 2012; 32: 4023–4026.
58. Wendling D, Vidon C, Godfrin-Valnet M, et al. Exacerbation of combined pulmonary fibrosis and emphysema syndrome during tocilizumab therapy for rheumatoid arthritis. *Joint Bone Spine* 2013; 80: 670–671.
59. Wada T, Akiyama Y, Yokota K, et al. A case of rheumatoid arthritis complicated with deteriorated interstitial pneumonia after the administration of abatacept. *Nihon Rinsho Meneki Gakkai Kaishi* 2012; 35: 433–438.