

Lung disease in rheumatoid arthritis. Challenges and opportunities

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Summary

The lungs and pleura are frequently sites of extra-articular involvement in rheumatoid arthritis (RA). Pleural disease and pulmonary nodules occur relatively frequently in the course of RA, and often are manageable by medical or surgical approaches. RA patients may develop both obstructive and restrictive lung disease. Obstructive lung disease may develop due to bronchiectasis, small airway disease (constrictive and follicular bronchiolitis), and cricoarytenoid involvement. Restrictive lung disease due to a diffuse fibrotic interstitial pneumonia (usually caused by the usual interstitial pneumonia or the non-specific interstitial pneumonia patterns) occurs in around 17% of RA patients throughout the course of the disease. The treatment of RA-associated interstitial lung disease is challenging. Although immunosuppressive medications and cytotoxic agents are often used to treat RA-associated interstitial pneumonia, there is no convincing evidence that any of the available drugs alter disease course or improve lung function. RA-associated obstructive and restrictive lung diseases profoundly affect patient wellbeing, response to therapy, choice of immunosuppression, and overall survival. Recent advances in the understanding of RA pathogenesis, the increased appreciation of cigarette smoke as a key predisposing factor of seropositive RA, and the emergence of novel biologic therapies hold promise for the development of more effective preventative and therapeutic strategies for lung complications in RA.

KEY WORDS: *rheumatoid arthritis; interstitial lung disease; cigarette smoking; autoimmunity.*

Lung disease manifestations in rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by joint inflammation and varying degrees of extra-articular involvement. RA affects approximately 1% of the population and markedly impacts quality of life and survival (1). While most patients have disease limited to the joints, other patients have prominent extra-articular RA manifestations which may or may not be accompanied by articular disease of equivalent severity (2-4). RA-associated lung disease is a relatively common and important extra-articular manifestation, and may occur in up to 50% of patients throughout the course of disease (3, 5-8). RA-associated lung disease can manifest itself in different clinical contexts by involving different lung compartments (airways, lung parenchyma, pleura etc). This review will summarize clinical, pathogenetic and management aspects of RA-associated lung disease.

Interstitial lung disease

Several patterns of interstitial lung disease (ILD) have been described in RA (3, 5, 9). ILD is more prevalent in smokers and seropositive RA patients than seronegative patients (2, 10-12). The most prevalent interstitial injury patterns described include usual interstitial pneumonia (UIP), non-specific interstitial pneumonia (NSIP), and organizing pneumonia (Figure 1) (5, 9, 12). Less commonly, desquamative interstitial pneumonia and other diffuse injury patterns occur in RA (Figure 1) (12). UIP is the most common histopathologic lesion associated with fibrotic interstitial lung disease in RA (5, 9, 13). The histopathologic pattern of RA-associated UIP is generally indistinguishable from idiopathic UIP (idiopathic pulmonary fibrosis or IPF), although detailed immunohistochemical analysis of RA-associated UIP shows significantly greater interstitial and peri-bronchiolar infiltration with immune cells compared to idiopathic UIP (14). Fibroblastic foci may be less prevalent in RA-associated UIP compared to idiopathic UIP (15, 16). Radiographically, RA-associated UIP and NSIP are usually indistinguishable from the corresponding idiopathic forms of interstitial pneumonia (9, 13). The prevalence of diffuse interstitial lung disease in RA is not fully defined. Retrospective analyses suggest an overall lifetime prevalence of approximately 17% (6). The natural course and response to therapy of RA-associated ILD are also not well defined. While organizing pneumonia occurring in RA is generally corticosteroid responsive, many of the other

Detailed immunohistochemical analysis of RA-associated UIP shows significantly greater interstitial and peri-bronchiolar infiltration with immune cells compared to idiopathic UIP.

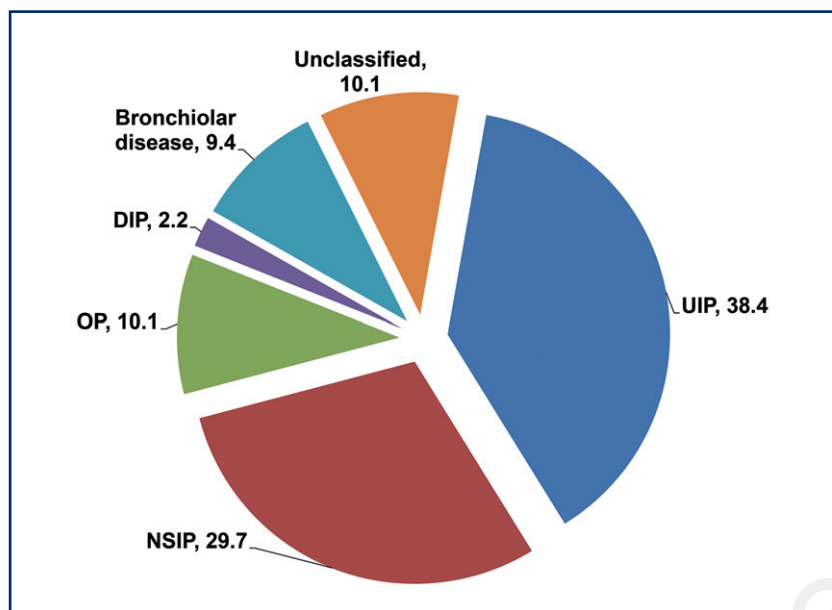


Figure 1 - Summary of lung biopsy findings in RA patients with diffuse lung disease.

The Venn diagram shows proportional distribution of lung biopsy findings in the published series on RA-associated diffuse lung disease [(abstracted from references (9, 12, 41, 71, 72)]. The numbers refer to percentage. UIP=usual interstitial pneumonia, NSIP=non-specific interstitial pneumonia, OP=organizing pneumonia, DIP=desquamate interstitial pneumonia. Unclassified=includes a mixture of pathologies including non-specific granulomatous reaction; granulomatous vasculitis; lymphoid hyperplasia; and localized pulmonary fibrosis.

histopathologic injury patterns associated with RA are partially, or non-responsive to corticosteroid or other immunosuppressive therapy. The natural history and prognosis of RA-associated fibrotic ILD due to UIP or NSIP have never been prospectively defined. Retrospective analyses suggest that that RA-associated UIP has a worse prognosis than RA-associated NSIP (5, 9, 12).

Airway disease

Bronchiectasis are present in 35% of patients with early RA, suggesting that autoimmunity rather than chronic immunosuppression is more likely a cause of large airway disease. RA patients with bronchiectasis may have a shorter life span than RA patients without.

Obstructive lung disease (defined as a forced expiratory volume in 1 second / forced vital capacity or FEV₁/FVC <70) is significantly more prevalent in RA patients than in the general population even after adjusting for smoking (T Bongartz et al. manuscript under review). Obstructive lung disease in RA may be due to diseases affecting the large airways such as bronchiectasis and cricoarytenoid joint involvement, or small airway diseases due to follicular, constrictive or mixed bronchiolitis (17-19).

Large airway involvement due to bronchiectasis is frequently identified by chest CT in RA patients throughout the course of disease (8, 20). Small airway involvement (bronchiolitis) is less common and accurate estimates of prevalence in RA are not available (18, 19). The chest high resolution computed tomography scan (HRCT scan) is critical in the evaluation and characterization of small and larger airway disease. A constrictive bronchiolitis may be diagnosed in RA patients with obstructive lung disease on pulmonary function testing, and chest CT findings of bronchial wall thickening with mosaic attenuation (18, 19). A follicular or mixed follicular / constrictive bronchiolitis occurs rarely in RA, and lung biopsy may be necessary for de-

finite diagnosis (18, 19). The cause for the increased incidence of bronchiectasis in RA is unclear, and potentially may be related to chronic infection / bacterial colonization and chronic immunosuppression induced by various medications to treat RA. However, a recent study showed HRCT evidence of bronchiectasis in 35% of patients with early RA (7), suggesting that autoimmunity rather than chronic immunosuppression is more likely a cause of large airway disease. It is possible that RA patients with bronchiectasis have a shorter life span than RA patients without (17).

Pleural disease

Pleurisy and effusions are common in RA. Pleural involvement is often painful and may be associated with an exudative pleural effusion which characteristically has a low glucose level and pH <7.20 (21). Cellular analysis of pleural effusions shows lymphocytic predominance (21). Rheumatoid factor levels in RA-related effusions may be very high, and when present, are very suggestive of a rheumatoid origin for the effusion (21, 22). Chylous pleural effusions have also been reported to occur in RA (21).

High rheumatoid factor levels in pleural effusions are very suggestive of a rheumatoid origin for the effusion.

Rheumatoid lung nodules

Rheumatoid nodules occur relatively frequently in skin and subcutaneous tissues of RA patients. Nodules also occur in the lungs and may cause diagnostic difficulty with lung cancer, especially in patients with a smoking history. Other clinical differential considerations include infection (especially fungal and mycobacterial) and vasculitic conditions like granulomatosis with polyangiitis (Wegener's granulomatosis). Rheumatoid lung nodules are often located in the subpleural regions and histologically are characterized by palisading histiocytes and giant cells (23). Positron Emission Tomography (PET) is

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not helpful in the clinical differentiation of RA lung nodules and lung cancer, as many are false positives (Standardized Uptake Values >2.5) (24). There is no consensus regarding management of pulmonary nodules in RA patients. The authors use Fleischner criteria to follow up these nodules (25). Biopsy, surgical resection and/or close radiologic follow up with chest CT is indicated in patients with nodules >1.0cm in size, especially if there is a prior history of smoking.

A proportion of RA patients experiences extra-articular manifestations years prior to the onset of joint symptoms.

and cyclic citrullinated peptides (CCP) are frequently obtained in an attempt to identify an underlying rheumatologic process, even in the absence of joint symptoms. It is now well recognized that some patients with ILD have positive titers of either or both RF and CCP antibodies but do not have articular symptoms. The interpretation of positive RF or CCP titers in this context is an area of some controversy: while some experts regard these patients as having “lung-dominant” rheumatoid disease (37), others consider these patients as simply having ILD with positive RF and CCP antibodies of indeterminate clinical significance.

A representative clinical case recently seen in our clinic was of a 77-year-old female whose primary complaint was progressive dyspnea on exertion. On physical examination, fine crackles were heard in the lung bases, and serologic evaluation showed markedly positive RF and CCP serologies. She denied any arthritic symptoms. Her chest CT scan showed evidence of bilateral subpleural reticular opacities associated with traction bronchiectasis without any definite honeycombing (Figure 2). X-rays of the hands did not show any erosive arthropathy. The patient did not meet American College of Rheumatology criteria for RA (38). This case raises a few questions. Does the patient have a lung-dominant form of RA without articular disease? Is this an idiopathic interstitial pneumonia with co-incidental positive RF and CCP? Does it matter? Is the treatment any different because of a positive antibody test?

Recent observations provide a starting point from which these questions may be addressed. While the cause of RA remains unknown, it is now apparent that serologic evidence of autoimmunity (RF and CCP antibodies) may predate the onset of articular symptoms by many years (39, 40). Thus it is very plausible that a proportion of RA patients will experience extra-articular manifestations years prior to the onset of joint symptoms. A recent study by Fischer and colleagues described a cohort of 74 individuals with anti-CCP antibodies and lung disease in the absence of articular disease (41). Radiographic characterization of the lung disease showed airway disease in 54%, isolated ILD in 14%, mixed interstitial and airway disease in 25%, and combined fibrosis and emphysema in 7% (41). That study showed that only 3 individuals developed articular manifestation of RA during the study period (median follow up of 449 days), and all had significantly elevated CCP titres that ranged from 92 to 175IU (41). These observations imply that autoimmunity associated with RA may occur in the absence of articular manifestations, at least early in the disease course. It is possible that cigarette smoke and other injuries to the airways and lung parenchyma may precipitate the onset of lung-dominant RA in certain individuals. Whether the lung itself may be the site of the initial development of RA-specific autoimmunity, and the potential role of smoking in the induction of injury and development of autoimmunity, are hypotheses that are currently under investigation (Taneja and Vassallo, manuscript in preparation).

Drug-induced toxicity

Many case reports and case series describe the development or worsening of established ILD in RA patients on anti-TNF α therapy. These studies raise caution regarding the use of TNF α inhibitors in RA patients with established ILD.

Many of the medications used to treat articular RA have the potential of inducing lung toxicity that usually manifests with diffuse lung infiltrates. The potential of medication-induced pulmonary toxicity must always be considered in the differential diagnosis of diffuse lung infiltrates, especially with patients on methotrexate therapy (26). A pneumonitis associated with methotrexate use has been reported to occur in up to 5% of RA patients; however it is

very uncommon with doses <20mg per week (27, 28). The use of tumor necrosis factor alpha (TNF α) inhibitors in RA has also been associated with the development of diffuse lung disease (29). Many case reports and case series describe the development or worsening of established ILD in RA patients on anti-TNF α therapy (29-31). These studies raise caution regarding the use of TNF α inhibitors in RA patients with established ILD. Although a definitive link between the use of TNF α inhibitors and ILD development has never been established, it is prudent to avoid these agents in RA patients with established lung disease and consider alternative treatment options. The overall risk of *de novo* ILD development with TNF α inhibitors is however likely very low, as shown in an analysis of 5000 patients with RA treated with TNF α inhibitors in Japan that reported a 0.5% occurrence of ILD over a 6 month period following the initiation of infliximab (32). Leflunomide, sulphasalazine and other medications used to treat RA have also been associated with pulmonary toxicity (33, 34). A prior history of ILD and prior methotrexate use seems to increase the risk of lung toxicity from leflunomide and TNF α inhibitor therapy (35, 36).

Rheumatoid lung disease without arthritis

In the initial clinical evaluation of patients with diffuse interstitial infiltrates, antibodies to rheumatoid factor (RF)

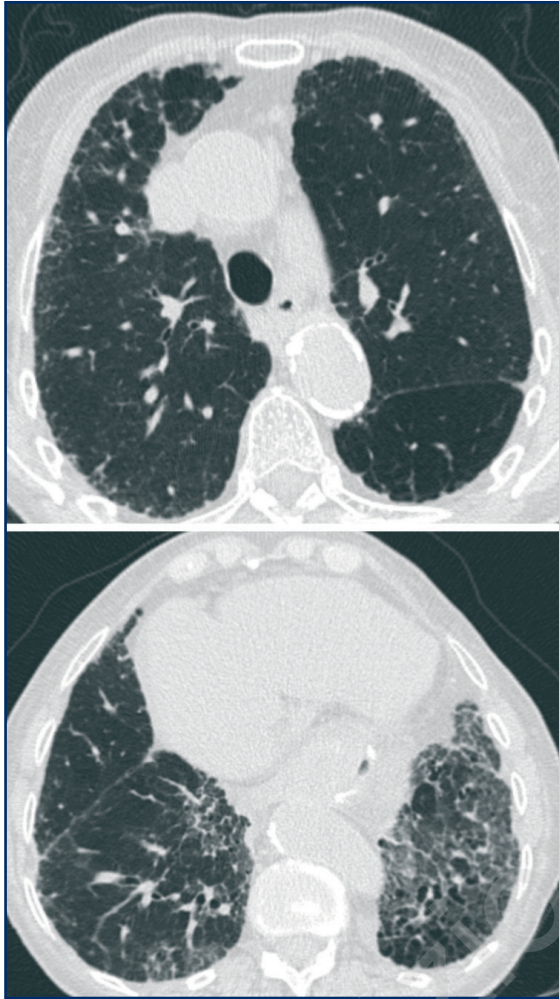


Figure 2 - Lung-dominant RA. Representative chest CT image findings in a patient with diffuse interstitial lung disease with positive CCP antibody and no clinical arthritis or radiographic joint erosions. The representative image from the upper lobe (upper panel) shows bilateral subpleural reticular opacities. The representative image from the lower lobes (lower panel) shows subpleural reticular opacities associated with traction bronchiectasis.

Treatment of rheumatoid lung diseases: challenges and opportunities

RA patients with bronchiectasis should be managed in an identical fashion as those with idiopathic bronchiectasis. RA lung nodules typically do not cause symptoms or lung function impairment and usually do not require specific therapy.

The treatment of RA-associated diffuse lung diseases is challenging. Whether therapy of articular and systemic inflammation alters the natural course of RA-associated lung manifestations is unknown. Treatment should be individu-

alized to each patient depending on the type of RA-lung manifestation, the severity of lung dysfunction, the extent of pulmonary symptoms, and patient tolerability to available immunosuppressive agents. All active smokers with RA should be counseled to stop smoking and be advised of the link between smoking and RA (Figure 3) (42-46).

Suspected drug-induced pulmonary reactions should first be managed by withdrawal of the offending drug. The role of corticosteroid therapy in the context of suspected drug-induced interstitial pulmonary toxicity is unclear, although it may be used in more severe cases to expedite recovery. Pleural disease and effusions generally respond to first and second-line agents used to treat articular RA, including prednisone and methotrexate. In some instances, surgical management with pleurodesis may be necessary in large or complex effusions.

RA patients with bronchiectasis should be managed in an identical fashion as those with idiopathic bronchiectasis. RA lung nodules typically do not cause symptoms or lung function impairment and usually do not require specific therapy. It is interesting to note a recent case report that showed reduction in size of pulmonary nodules following therapy with an interleukin-6 blocking agent (47).

Treatment of RA-associated ILD is particularly challenging. Corticosteroid therapy is generally ineffective in the management of RA-associated UIP. Whether corticosteroid therapy improves lung function in RA-associated NSIP is unclear, and has never been demonstrated. Methotrexate is generally avoided in this context due to the potential of inducing a pulmonary drug reaction that may be impossible to distinguish from progression of the underlying diffuse lung disease. The roles of azathioprine and mycophenolate mofetil are unclear, but anecdotal experience suggests limited efficacy. Cyclophosphamide has been demonstrated to modestly improve lung function and slow the rate of lung function decline in patients with scleroderma-related ILD (48), but its role in RA-ILD has never been studied prospectively or in a randomized fashion. N-acetylcysteine, an anti-oxidant that may have a very modest impact on the rate of decline of lung function in idiopathic pulmonary fibrosis (49), is sometimes also used to treat RA-ILD, but evidence in support of its use is also lacking. Rituximab, an antibody that binds the CD20 surface receptor on B cells and induces depletion of antibody-forming cells, has been tested in a small open-label study of 8 RA patients with ILD (50). Although chest CT imaging and pulmonary function testing showed stability in most patients over the 48 week period of the study, there were two recorded deaths in this group (50). The absence of a clear therapeutic pathway for patients with RA-ILD provides opportunity for investigation and design of new clinical trials aimed at identifying new treatment approaches for these patients. In this context, further research on the basic mechanisms of disease development in RA associated ILD are urgently needed. The availability of several new agents such as inhibitors of interleukin-6 (51), interleukin-17 (52), spleen tyrosine kinase (Syk) (53), and Janus associated kinase (JAK) (54) also provide an array of new therapeutic options that may be considered in the management of RA-associated interstitial disease.

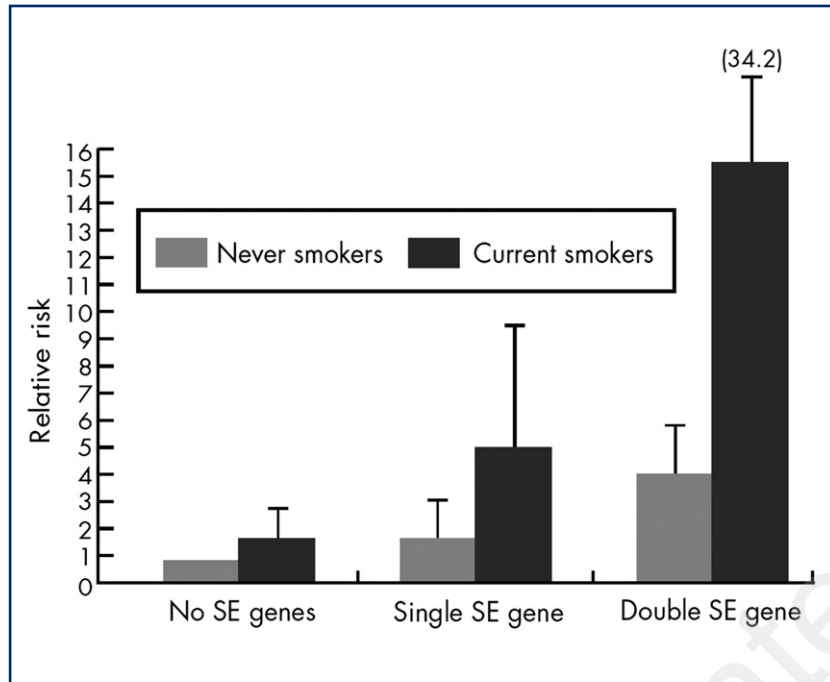


Figure 3 - Smoking and host genetic factors co-operate in the induction of seropositive RA. Graph representing the combined effect of smoking and different numbers of shared epitope (SE) alleles (0-2) on the relative risk of developing seropositive RA. Figure reproduced with permission from reference (46).

Cigarette smoke and RA

It is now well established that cigarette smoke is a preventable risk factor for RA (46, 55-58). Cumulative exposure to cigarette smoke (pack years smoked) and host genetic factors interact in this predisposition to RA. For example, one study showed that the odds ratio of developing RA after having smoked 41-50 pack years is 13.54 (95% confidence interval 2.89 to 63.38) (59). Another study showed that individuals with RA who smoked >25 pack years were 3.1 times more likely to be RF positive and 2.4 times more likely to have joint erosions than non-smokers, suggesting that cumulative cigarette smoke exposure influences development of autoimmunity and the severity of articular RA (10). Padyukov et al (57) showed that genetic factors [human leukocyte antigen-DR alleles encoding the so-called shared epitope (SE)] and cigarette smoking interact to markedly increase an individual's risk of developing seropositive RA (Figure 3). While the epidemiologic association between smoking and RA is quite apparent, the mechanisms by which smoking mediates RA-specific autoimmunity are not well understood. Cigarette smoke influences immunity in complex ways. Both immune stimulatory and suppressive functions of cigarette smoke have been described. For example, cigarette smoke and cigarette smoke extracts have been shown to both stimulate and suppress certain dendritic cell functions (60-63). Dendritic cells obtained from mice chronically exposed to cigarette smoke or exposed to extracts from cigarette smoke show diminished T helper (Th)-1 cell cytokine production following activation with stimulants like bacterial lipopolysaccharide (60, 61, 63). On the other hand, cigarette smoke challenged dendritic cells produce an excess of prostaglandins and inflammatory chemokines like CXCL8 (62), and survive longer *in vitro* (64). Cigarette smoke has also been associated with an elevated ratio TNF α /STNFR

released by immune cells, resulting in augmentation of TNF α activity in RA patients who smoke (65). Cigarette smoke may also preferentially promote the induction of T lymphocytes polarized to preferentially secrete pro-inflammatory Th-17 type cytokines (66-68).

Cigarette smoke also affects protein citrullination, a process by which post-translational modification of arginine residues in a protein are converted into citrulline (69). This process is not only restricted to synovial tissue in RA patients but can also occur in extra-articular tissues and has also been observed in patients with interstitial pneumonia and nodules (56, 70). Smoking is associated with increased citrullination of protein in the lung, which is likely mediated by enhanced activity of smoking-induced peptidylarginine deiminase (PAD) enzymes (56). Based on epidemiological studies in humans, and studies in murine models, it may be speculated that cigarette smoke-induced modulation of antigen presenting cell function promotes autoimmunity by modifying presentation of autologous proteins *via* certain (HLA) molecules. Smoking may be a critical signal to convert the asymptomatic and genetically predisposed individuals to develop clinical signs of disease. Studies are underway to delineate the interaction between smoking and specific HLA genes that have been shown to co-operate in the predisposition to RA. In a scenario where smoking induces influx of activated T cells to areas of tissue damage (for example the lung during an infection), there may be availability of autologous proteins like vimentin whose modification by citrullination and subsequent presentation may lead to an autoreactive response. Vimentin is a potentially highly relevant protein in this context as it is secreted by macrophages that are present in greater numbers in the lungs of smokers. Understanding specific mechanisms by which smoking and host genetic factors interact in the development of RA is critical in the development of novel targets for therapy.

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References

1. Linos A, Worthington JW, O'Fallon WM, Kurland LT. The epidemiology of rheumatoid arthritis in Rochester, Minnesota: a study of incidence, prevalence, and mortality. *Am J Epidemiol* 1980 Jan; 111(1):87-98.
2. Doyle JJ, Eliasson AH, Argyros GJ, Dennis GJ, Finger DR, Hurwitz KM, et al. Prevalence of pulmonary disorders in patients with newly diagnosed rheumatoid arthritis. *Clin Rheumatol* 2000;19(3):217-21.
3. Nannini C, Ryu JH, Matteson EL. Lung disease in rheumatoid arthritis. *Curr Opin Rheumatol* 2008 May;20(3):340-6.
4. Turesson C, Jacobsson L, Bergstrom U. Extra-articular rheumatoid arthritis: prevalence and mortality. *Rheumatology* 1999 Jul;38(7):668-74.
5. Kim EJ, Collard HR, King TE, Jr. Rheumatoid arthritis-associated interstitial lung disease: the relevance of histopathologic and radiographic pattern. *Chest* 2009 Nov;136(5):1397-405.
6. Bongartz T, Nannini C, Medina-Velasquez YF, Achenbach SJ, Crowson CS, Ryu JH, et al. Incidence and mortality of interstitial lung disease in rheumatoid arthritis: A population based study. *Arthritis Rheum* 2010 Feb 12;62(6):1583-91.
7. Wilsher M, Voight L, Milne D, Teh M, Good N, Kolbe J, et al. Prevalence of airway and parenchymal abnormalities in newly diagnosed rheumatoid arthritis. *Respir Med* 2012 Oct;106(10):1441-6.
8. Lieberman-Maran L, Orzano IM, Passero MA, Lally EV. Bronchiectasis in rheumatoid arthritis: report of four cases and a review of the literature—implications for management with biologic response modifiers. *Semin Arthritis Rheum* 2006 Jun;35(6):379-87.
9. Lee HK, Kim DS, Yoo B, Seo JB, Rho JY, Colby TV, et al. Histopathologic pattern and clinical features of rheumatoid arthritis-associated interstitial lung disease. *Chest* 2005 Jun;127(6):2019-27.
10. Saag KG, Cerhan JR, Kolluri S, Ohashi K, Hunninghake GW, Schwartz DA. Cigarette smoking and rheumatoid arthritis severity. *Ann Rheum Dis* 1997 Aug;56(8):463-9.
11. Westedt ML, Hazes JM, Breedveld FC, Sterk PJ, Dijkman JH. Cigarette smoking and pulmonary diffusion defects in rheumatoid arthritis. *Rheumatology International* 1998;18(1):1-4.
12. Nakamura Y, Suda T, Kaida Y, Kono M, Hozumi H, Hashimoto D, et al. Rheumatoid lung disease: prognostic analysis of 54 biopsy-proven cases. *Respir Med* 2012 Aug;106(8):1164-9.
13. Kim EJ, Elicker BM, Maldonado F, Webb WR, Ryu JH, Van Uden JH, et al. Usual interstitial pneumonia in rheumatoid arthritis-associated interstitial lung disease. *Eur Respir J* 2009 Dec 8.
14. Turesson C, Matteson EL, Colby TV, Vuk-Pavlovic Z, Vassallo R, Weyand CM, et al. Increased CD4+ T cell infiltrates in rheumatoid arthritis-associated interstitial pneumonitis compared with idiopathic interstitial pneumonitis. *Arthritis Rheum* 2005 Jan;52(1):73-9.
15. Enomoto N, Suda T, Kato M, Kaida Y, Nakamura Y, Imokawa S, et al. Quantitative analysis of fibroblastic foci in usual interstitial pneumonia. *Chest* 2006 Jul;130(1):22-9.
16. Flaherty KR, Colby TV, Travis WD, Toews GB, Mumford J, Murray S, et al. Fibroblastic foci in usual interstitial pneumonia: idiopathic versus collagen vascular disease. *Am J Respir Crit Care Med* 2003 May 15;167(10):1410-5.
17. Swinson DR, Symmons D, Suresh U, Jones M, Booth J. Decreased survival in patients with co-existent rheumatoid arthritis and bronchiectasis. *Br J Rheumatol* 1997 Jun;36(6):689-91.
18. Devouassoux G, Cottin V, Liote H, Marchand E, Frachon I, Schuller A, et al. Characterisation of severe obliterative bronchiolitis in rheumatoid arthritis. *Eur Respir J* 2009 May;33(5):1053-61.
19. Yousem SA, Colby TV, Carrington CB. Follicular bronchitis/bronchiolitis. *Hum Pathol* 1985 Jul; 16(7):700-6.
20. Hassan WU, Keaney NP, Holland CD, Kelly CA. High resolution computed tomography of the lung in lifelong non-smoking patients with rheumatoid arthritis. *Ann Rheum Dis* 1995 Apr; 54(4): 308-10.
21. Balbir-Gurman A, Yigla M, Nahir AM, Braun-Moscovici Y. Rheumatoid pleural effusion. *Semin Arthritis Rheum* 2006 Jun;35(6):368-78.
22. Balbir-Gurman A, Guralnik L, Best LA, Vlodyavsky E, Yigla M, Menahem Nahir A, et al. Accelerated pulmonary nodulosis and sterile pleural effusion in a patient with psoriatic arthropathy during methotrexate therapy: a case report. *J Clin Rheumatol* 2009 Feb;15(1):29-30.
23. Schneider F, Gruden J, Tazelaar HD, Leslie KO. Pleuropulmonary pathology in patients with rheumatic disease. *Arch Pathol Lab Med* 2012 Oct;136(10):1242-52.
24. Saraya T, Tanaka R, Fujiwara M, Koji H, Oda M, Ogawa Y, et al. Fluorodeoxyglucose (FDG) uptake in pulmonary rheumatoid nodules diagnosed by video-assisted thoracic surgery lung biopsy: two case reports and a review of the literature. *Mod Rheumatol* 2012 Jun 6.
25. MacMahon H, Austin JH, Gamsu G, Herold CJ, Jett JR, Naidich DP, et al. Guidelines for management of small pulmonary nodules detected on CT scans: a statement from the Fleischner Society. *Radiology* 2005 Nov;237(2):395-400.
26. Carroll GJ, Thomas R, Phatouros CC, Atchison MH, Leslie AL, Cook NJ, et al. Incidence, prevalence and possible risk factors for pneumonitis in patients with rheumatoid arthritis receiving methotrexate. *J Rheumatol* 1994 Jan;21(1):51-4.
27. Jordan SR, Stevanovic VR, Herbison P, Dockerty J, Highton J. Methotrexate pneumonitis in rheumatoid arthritis: increased prevalence with increasing latitude: an epidemiological study of trends in New Zealand. *J Clin Rheumatol* 2011 Oct;17(7):356-7.
28. Saravanan V, Kelly C. Drug-related pulmonary problems in patients with rheumatoid arthritis. *Rheumatology* 2006 Jul;45(7):787-9.
29. Perez-Alvarez R, Perez-de-Lis M, Diaz-Lagares C,

- Pego-Reigosa JM, Retamozo S, Bove A, et al. Interstitial lung disease induced or exacerbated by TNF-targeted therapies: analysis of 122 cases. *Semin Arthritis Rheum* 2011 Oct;41(2):256-64.
30. Taki H, Kawagishi Y, Shinoda K, Hounoki H, Ogawa R, Sugiyama E, et al. Interstitial pneumonitis associated with infliximab therapy without methotrexate treatment. *Rheumatology International* 2009 Dec;30(2):275-6.
31. Villeneuve E, St-Pierre A, Haraoui B. Interstitial pneumonitis associated with infliximab therapy. *J Rheumatol* 2006 Jun;33(6):1189-93.
32. Takeuchi T, Tatsuki Y, Nogami Y, Ishiguro N, Tanaka Y, Yamanaka H, et al. Postmarketing surveillance of the safety profile of infliximab in 5000 Japanese patients with rheumatoid arthritis. *Ann Rheum Dis* 2007/07/24 ed2008. p. 189-94.
33. Karmakar GC, Wong CA, Horwood F, Anderson G. Sulphasalazine lung toxicity: report of two cases. *N Z Med J* 2010 Aug 13;123(1320):86-7.
34. Alcorn N, Saunders S, Madhok R. Benefit-risk assessment of leflunomide: an appraisal of leflunomide in rheumatoid arthritis 10 years after licensing. *Drug Safety* 2009;32(12):1123-34.
35. Suissa S, Hudson M, Ernst P. Leflunomide use and the risk of interstitial lung disease in rheumatoid arthritis. *Arthritis Rheum* 2006 May;54(5):1435-9.
36. Thavarajah K, Wu P, Rhew EJ, Yeldandi AK, Kamp DW. Pulmonary complications of tumor necrosis factor-targeted therapy. *Respir Med* 2009 May;103(5):661-9.
37. Fischer A, West SG, Swigris JJ, Brown KK, du Bois RM. Connective tissue disease-associated interstitial lung disease: a call for clarification. *Chest* 2010 Aug;138(2):251-6.
38. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988 Mar;31(3):315-24.
39. Majka DS, Deane KD, Parrish LA, Lazar AA, Baron AE, Walker CW, et al. Duration of preclinical rheumatoid arthritis-related autoantibody positivity increases in subjects with older age at time of disease diagnosis. *Ann Rheum Dis* 2008 Jun;67(6):801-7.
40. Rantapaa-Dahlqvist S, de Jong BA, Berglin E, Hallmans G, Wadell G, Stenlund H, et al. Antibodies against cyclic citrullinated peptide and IgA rheumatoid factor predict the development of rheumatoid arthritis. *Arthritis Rheum* 2003 Oct;48(10):2741-9.
41. Fischer A, Solomon JJ, du Bois RM, Deane KD, Olson AL, Fernandez-Perez ER, et al. Lung disease with anti-CCP antibodies but not rheumatoid arthritis or connective tissue disease. *Respir Med* 2012 Jul;106(7):1040-7.
42. Albano SA, Santana-Sahagun E, Weisman MH. Cigarette smoking and rheumatoid arthritis. *Semin Arthritis Rheum* 2001 Dec;31(3):146-59.
43. Criswell LA, Merlino LA, Cerhan JR, Mikuls TR, Mudano AS, Burma M, et al. Cigarette smoking and the risk of rheumatoid arthritis among postmenopausal women: results from the Iowa Women's Health Study. *Am J Med* 2002 Apr 15;112(6):465-71.
44. Finckh A, Dehler S, Costenbader KH, Gabay C. Cigarette smoking and radiographic progression in rheumatoid arthritis. *Ann Rheum Dis* 2007 Aug;66(8):1066-71.
45. Harrison BJ. Influence of cigarette smoking on disease outcome in rheumatoid arthritis. *Curr Opin Rheumatol* 2002 Mar;14(2):93-7.
46. Klareskog L, Alfredsson L, Rantapaa-Dahlqvist S, Berglin E, Stolt P, Padyukov L. What precedes development of rheumatoid arthritis? *Ann Rheum Dis* 2004 Nov;63 Suppl 2:ii28-ii31.
47. Andres M, Vela P, Romera C. Marked improvement of lung rheumatoid nodules after treatment with tocilizumab. *Rheumatology* 2012 Jun;51(6):1132-4.
48. Tashkin DP, Elashoff R, Clements PJ, Goldin J, Roth MD, Furst DE, et al. Cyclophosphamide versus placebo in scleroderma lung disease. *N Engl J Med* 2006 Jun 22;354(25):2655-66.
49. Demedts M, Behr J, Buhl R, Costabel U, Dekhuijzen R, Jansen HM, et al. High-dose acetylcysteine in idiopathic pulmonary fibrosis. *N Engl J Med*. 2005 Nov 24;353(21):2229-42.
50. Matteson EL BT, Ryu JH, Crowson CS, Hartman TE, Dellaripa PF. Open-Label, Pilot Study of the Safety and Clinical Effects of Rituximab in Patients with Rheumatoid Arthritis-Associated Interstitial Pneumonia. *Open Journal of Rheumatology and Autoimmune Diseases* 2012;2:53-58.
51. Navarro-Millan I, Singh JA, Curtis JR. Systematic review of tocilizumab for rheumatoid arthritis: a new biologic agent targeting the interleukin-6 receptor. *Clinical Therapeutics* 2012 Apr;34(4):788-802 e3.
52. van den Berg WB, Miossec P. IL-17 as a future therapeutic target for rheumatoid arthritis. *Nat Rev Rheumatol* 2009 Oct;5(10):549-53.
53. Weinblatt ME, Kavanaugh A, Genovese MC, Mussler TK, Grossbard EB, Magilavy DB. An oral spleen tyrosine kinase (Syk) inhibitor for rheumatoid arthritis. *N Engl J Med* 2010 Sep 30;363(14):1303-12.
54. Tanaka Y, Maeshima Y, Yamaoka K. In vitro and in vivo analysis of a JAK inhibitor in rheumatoid arthritis. *Ann Rheum Dis* 2012 Apr;71 Suppl 2:i70-4.
55. Kallberg H, Ding B, Padyukov L, Bengtsson C, Ronnelid J, Klareskog L, et al. Smoking is a major preventable risk factor for rheumatoid arthritis: estimations of risks after various exposures to cigarette smoke. *Ann Rheum Dis* 2011 Mar;70(3):508-11.
56. Makrygiannakis D, Hermansson M, Ulfgren AK, Nicholas AP, Zendman AJ, Eklund A, et al. Smoking increases peptidylarginine deiminase 2 enzyme expression in human lungs and increases citrullination in BAL cells. *Ann Rheum Dis* 2008 Oct; 67(10):1488-92.
57. Padyukov L, Silva C, Stolt P, Alfredsson L, Klareskog L. A gene-environment interaction between smoking and shared epitope genes in HLA-DR provides a high risk of seropositive rheumatoid arthritis. *Arthritis Rheum* 2004 Oct;50(10):3085-92.
58. Stolt P, Bengtsson C, Nordmark B, Lindblad S, Lundberg I, Klareskog L, et al. Quantification of the influence of cigarette smoking on rheumatoid arthritis: results from a population based case-control study, using incident cases. *Ann Rheum Dis* 2003 Sep;62(9):835-41.

59. Hutchinson D, Shepstone L, Moots R, Lear JT, Lynch MP. Heavy cigarette smoking is strongly associated with rheumatoid arthritis (RA), particularly in patients without a family history of RA. *Ann Rheum Dis* 2001 Mar;60(3):223-7.
60. Kroening PR, Barnes TW, Pease L, Limper A, Kita H, Vassallo R. Cigarette smoke-induced oxidative stress suppresses generation of dendritic cell IL-12 and IL-23 through ERK-dependent pathways. *J Immunol* 2008 Jul 15;181(2):1536-47.
61. Vassallo R, Tamada K, Lau JS, Kroening PR, Chen L. Cigarette smoke extract suppresses human dendritic cell function leading to preferential induction of Th-2 priming. *J Immunol* 2005 Aug 15; 175(4): 2684-91.
62. Vassallo R, Kroening PR, Parambil J, Kita H. Nicotine and oxidative cigarette smoke constituents induce immune-modulatory and pro-inflammatory dendritic cell responses. *Mol Immunol* 2008 Jul;45(12):3321-9.
63. Robbins CS, Dawe DE, Goncharova SI, Pouladi MA, Drannik AG, Swirski FK, et al. Cigarette smoke decreases pulmonary dendritic cells and impacts antiviral immune responsiveness. *Am J Respir Cell Mol Biol* 2004 Feb;30(2):202-11.
64. Vassallo R, Walters PR, Lamont J, Kottom TJ, Yi ES, Limper AH. Cigarette smoke promotes dendritic cell accumulation in COPD; a Lung Tissue Research Consortium study. *Respir Res* 2010 Apr 26;11(1):45.
65. Glossop JR, Dawes PT, Matthey DL. Association between cigarette smoking and release of tumour necrosis factor alpha and its soluble receptors by peripheral blood mononuclear cells in patients with rheumatoid arthritis. *Rheumatology* 2006 Oct; 45(10): 1223-9.
66. Harrison OJ, Foley J, Bolognese BJ, Long E, 3rd, Podolin PL, Walsh PT. Airway infiltration of CD4+ CCR6+ Th17 type cells associated with chronic cigarette smoke induced airspace enlargement. *Immunol Lett* 2008 Nov 16;121(1):13-21.
67. Onozaki K. Etiological and biological aspects of cigarette smoking in rheumatoid arthritis. *Inflamm Allergy Drug Targets* 2009 Dec;8(5):364-8.
68. Vargas-Rojas MI, Ramirez-Venegas A, Limon-Camacho L, Ochoa L, Hernandez-Zenteno R, Sansores RH. Increase of Th17 cells in peripheral blood of patients with chronic obstructive pulmonary disease. *Respir Med* 2011 Nov; 105(11): 1648-54.
69. van Venrooij WJ, Pruijn GJ. Citrullination: a small change for a protein with great consequences for rheumatoid arthritis. *Arthritis Res* 2000;2(4):249-51.
70. Bongartz T, Cantaert T, Atkins SR, Harle P, Myers JL, Turesson C, et al. Citrullination in extra-articular manifestations of rheumatoid arthritis. *Rheumatology (Oxford)* 2007 Jan;46(1):70-5.
71. Tanaka N, Kim JS, Newell JD, Brown KK, Cool CD, Meehan R, et al. Rheumatoid arthritis-related lung diseases: CT findings. *Radiology* 2004 Jul; 232(1): 81-91.
72. Hakala M, Paakko P, Huhti E, Tarkka M, Sutinen S. Open lung biopsy of patients with rheumatoid arthritis. *Clin Rheumatol* 1990 Dec;9(4):452-60.