Correspondence

Methotrexate Might Increase Mortality from Interstitial Lung Disease in Rheumatoid Arthritis

To the Editor:

We read with interest the article by Olson and coworkers (1). They described that tumor necrosis factor (TNF)-α antagonists might be detrimental in patients with rheumatoid arthritis (RA)-associated interstitial lung disease (ILD). Indeed, TNF-α antagonists can induce or exacerbate ILD in patients with RA, but they are often concomitantly administered with methotrexate (MTX), which has traditionally been associated with the development of drug-induced ILD (2). The reported incidence of ILD induced by MTX is apparently higher than that induced by TNF-α antagonists (2–4). In addition, MTX is the most commonly prescribed drug for patients with RA worldwide (4). We think that MTX has a larger impact than TNF-α antagonists on the development or exacerbation of ILD in patients with RA, and that this is the cause of increasing mortality from ILD in such patients. Further investigation is required to clarify this notion.

Author disclosures are available with the text of this letter at www.atsjournals.org.

Mikio Toyoshima, M.D., Ph.D.
Hamamatsu Rosai Hospital
Hamamatsu, Japan
and
Hamamatsu University School of Medicine
Hamamatsu, Japan

Kingo Chida, M.D., Ph.D.
Takafumi Suda, M.D., Ph.D.
Hamamatsu University School of Medicine
Hamamatsu, Japan

Masaki Sato, M.D., Ph.D.
Hamamatsu Rosai Hospital
Hamamatsu, Japan

References

1. Olson AL, Swigris JJ, Sprunger DB, Fischer A, Fernandez-Perez ER, Solomon J, Murphy J, Cohen M, Raghu G, Brown KK. Rheumatoid arthritis-interstitial lung disease-associated mortality. *Am J Respir Crit Care Med* 2011;183:372–378.
2. Perez-Alvarez R, Perez-de-Lis M, Diaz-Lagares C, Pego-Reigosa JM, Retamozo S, Bove A, Brito-Zeron P, Bosch X, Ramos-Casals M. Interstitial lung disease induced or exacerbated by TNF-targeted therapies: analysis of 122 cases. *Semin Arthritis Rheum* 2011;41:256–264.
3. Ohosone Y, Okano Y, Kameda H, Fujii T, Hama N, Hirakata M, Mimori T, Akizuki M, Ikeda Y. Clinical characteristics of patients with rheumatoid arthritis and methotrexate induced pneumonitis. *J Rheumatol* 1997;24:2299–2303.
4. Shidara K, Hoshi D, Inoue E, Yamada T, Nakajima A, Taniguchi A, Hara M, Momohara S, Kamatani N, Yamanaka H. Incidence of and risk factors for interstitial pneumonia in patients with rheumatoid arthritis in a large Japanese observational cohort, IORRA. *Mod Rheumatol* 2010;20:280–286.

Rheumatoid Arthritis and Pneumoconiosis

To the Editor:

The article by Olson and colleagues presented interesting statistics on mortality for rheumatoid arthritis–associated interstitial lung disease (RA-ILD) (1). However, no mention was made in the article of the well-known association between interstitial fibrosis caused by asbestos, coal, or silica and either rheumatoid arthritis or positive serum rheumatoid factor (2–6).

The methodology of Olson and coworkers, as noted in their discussion of limitations, was based on the accuracy of the diagnoses reported on death certificates. Given the known association between the pneumoconioses and rheumatoid arthritis it is likely that some percentage of the decedents identified with RA-ILD actually had interstitial disease from mineral exposure and also had rheumatoid arthritis, or that some had interstitial lung disease from mineral dust exposure and had a positive rheumatoid factor without rheumatoid arthritis rather than RA-ILD.

Data in the article by Olson and coworkers that would be consistent with the possibility of misdiagnosis include:

1. Mortality rates for RA-ILD decreased in men while they increased in women. Men are more likely to have pneumoconiosis, and mortality rates for silicosis, and for coal workers' pneumoconiosis are declining.
2. The occurrence of RA-ILD was higher in men than women (9.8% versus 6.8%), even though rheumatoid arthritis is more common in women. This difference between men and women is consistent with the increased incidence of pneumoconiosis in men versus women.

Further work that examines the occurrence and trends in RA-ILD should consider what role interstitial disease from exposure to mineral dust confounds the diagnosis and recognition of RA-ILD. Studies that involve more strict criteria for determining the presence of interstitial disease and rheumatoid arthritis would benefit from the inclusion of occupational histories/exposures in their case definitions.

Author disclosures are available with the text of this letter at www.atsjournals.org.

Kenneth D. Rosenman, M.D.
Michigan State University
East Lansing, Michigan

References

1. Olson AL, Swigris JJ, Sprunger DB, Fischer A, Fernandez-Perez ER, Solomon J, Murphy J, Cohen M, Raghu G, Brown KK. Rheumatoid arthritis–interstitial lung disease–associated mortality. *Am J Respir Crit Care Med* 2011;183:372–378.
2. Kart L, Sarikaya S, Gurel A, Altin R, Armutcu F, Tor M, Ozdolap S. Rheumatoid factor seropositivity and rheumatoid symptoms in coal worker's pneumoconiosis. *Clin Rheumatol* 2003;4–5:365–366.
3. Klockars M, Koskela RS, Jarvinen E, Kolari PJ, Rossi A. Silica exposure and rheumatoid arthritis: a follow up study of granite workers 1940–81. *Br Med J (Clin Res Ed)* 1987;294:997–1000.
4. Makol A, Reilly MJ, Rosenman KD. Prevalence of connective tissue disease in silicosis. *Am J Ind Med* 2011;54:255–262.
5. Stolt P, Kallberg H, Lundberg I, Sjogren B, Klareskog L, Alfredsson L. Silica exposure is associated with increased risk of developing rheumatoid arthritis: results from the Swedish EIRA study. *Ann Rheum Dis* 2005;64:582–586.
6. Turner-Warwick M, Parkes WR. Circulating rheumatoid and antinuclear factors in asbestos workers. *BMJ* 1970;3:492–495.

Supported by NIOSH 2 U60OH008466.