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Do Anti-TNF Blockers Increase the Risk of Lung Involvement in Patients with Ankylosing Spondylitis or Psoriatic Arthritis? A Systematic Review

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ABSTRACT: Lung involvement is a well-recognized extra-articular manifestation of ankylosing spondylitis (AS). Anecdotal reports suggest that the use of anti-TNF drugs may be related to lung disease and pulmonary fibrosis. To examine the association between anti-TNF drugs and the development of lung disease in patients with AS or psoriatic arthritis (PsA) we conducted a systematic review. Of the 670 papers identified by means of key word and hand search, only one full-text paper was considered potentially relevant but had to be discarded as it did not meet the eligibility criteria. Although no conclusion was reached, this is the first systematic review to examine this problem which is becoming increasingly important as these drugs are widely prescribed in patients with spondyloarthritis.

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KEY WORDS: ankylosing spondylitis (AS), psoriatic arthritis (PsA), anti-tumor necrosis factor (TNF), interstitial lung disease (ILD), pulmonary fibrosis

Lung involvement is a well-recognized extra-articular manifestation of ankylosing spondylitis (AS) [1], with a prevalence of 0–30%; the most frequent forms are upper lobe fibrosis, mycetoma formation and pleural thickening [1,2]. However, high resolution computed tomography (HRTC) findings indicate that its prevalence is as high as 61% in patients with long-standing AS [2], but there are few data concerning patients with psoriatic arthritis (PsA) [3]. Anti-tumor necrosis factor (TNF) blockers have been successfully used to treat patients with moderate and severe AS or PsA [4], but anecdotal reports suggest that their use may be related to lung disease and pulmonary fibrosis [4]. The aim of this study was to examine the association between anti-TNF drugs and the development of lung disease in patients with AS or PsA.

The review's protocol was registered with the international register of systematic reviews PROSPERO (http://www.crd.york.ac.uk/PROSPERO/) and followed the PRISMA guidelines. In order to be included, studies had to be reviews or observational cross-sectional, non-interventional, case-control or cohort studies evaluating the risk of pulmonary complications in patients exposed to anti-TNF blockers. The systematic search of the MEDLINE and EMBASE databases, which was extended to grey literature sources, used the following keywords/MeSH terms: psoriatic arthritis, ankylosing spondylitis, spondyloarthritis, anti-TNF blockers, infliximab, etanercept, adalimumab, interstitial lung disease, lung fibrosis, and pulmonary fibrosis. The study participants had to have a diagnosis of AS or PsA based on classification criteria or a rheumatologist's diagnosis; subjects with juvenile-onset AS or PsA were excluded. In order to be considered eligible, the papers had to report the prevalence of fibrosis or interstitial lung disease (ILD) in patients with AS or PsA treated with anti-TNF blockers.

The search covered a 34 year period (1 January 1980 to 30 September 2014) and was conducted by two investigators (E.G. and F.A.) who independently selected the potentially eligible studies. Disagreements were resolved by consensus; if no agreement could be reached a third investigator made the final decision. The data were individually extracted by F.A. and E.G. using a predefined extraction form. Figure 1 shows the study selection process. Of the 670 papers identified by means of the key word and hand search (189 from MEDLINE via PubMed, and 481 from EMBASE excluding the MEDLINE results), 669 were excluded as being irrelevant to the research question on the basis of their titles and abstracts. One full-text paper was considered potentially relevant but had to be discarded as it did not meet the eligibility criteria. There were therefore no published observational studies assessing the risk of lung fibrosis and ILD in patients exposed to anti-TNF blockers, and no conclusion could be reached. Although no conclusion was reached, this is the first systematic review to examine the association between AS/PsA and ILD or lung fibrosis in patients treated with anti-TNF blockers, which is becoming increasingly important as these drugs are widely prescribed to improve symptoms and functional status in patients with spondyloarthritis (SpA). TNFα is a key

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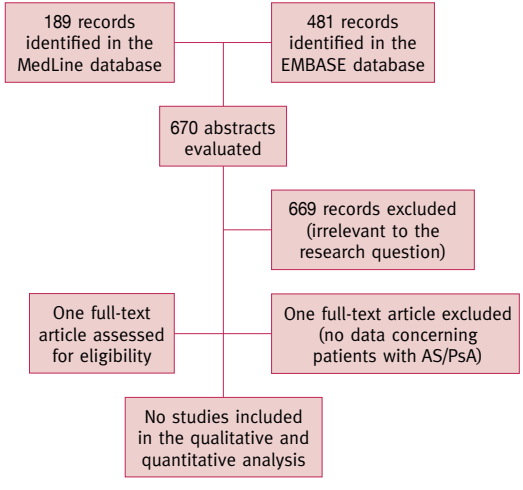
Figure 1. Study selection process



cytokine in the pathogenesis of ILD, playing a profibrotic role by up-regulation of pulmonary growth factor-beta 1 (TGFβ1) expression through extracellular regulated kinase-specific pathway activation in fibroblasts and regulation of p21 (cyclin-dependent kinase inhibitor). Furthermore, it is a key regulator of the cell cycle, DNA repair and aptosis and antifibrotic effects by inhibiting fibroblast proliferation and limiting lung inflammation. Treatment with anti-TNF blockers may result in pulmonary shifts toward anti-inflammatory cytokines, contributing to profibrotic changes. These may induce the exacerbation or induction of ILD, which contributes to worst prognosis and quality of life in patients with SpA with or without lung involvement.

Furthermore, anti-TNF therapy is associated with increased risk of reactivation of latent tuberculosis (TB), although the current recommendations designed to prevent this are effective. Thus, due to the higher prevalence of ILD, clinicians must be aware of the non-specific ILDs revealed by HRCT in otherwise asymptomatic SpA patients, which are undetectable by chest radiography and must not be confused with tuberculous lesions. Clearly, large controlled studies specifically designed to assess the pulmonary profile of anti-TNF blockers in clinical practice in SpA patients with or without previous ILD are warranted.

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