



Therapeutic management of patients with rheumatoid arthritis and associated interstitial lung disease: case report and literature review

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Abstract: Rheumatoid arthritis (RA) is an inflammatory autoimmune disease that can present different extrarticular manifestations involving heart, lungs and kidneys. In recent years there has been a growing awareness of the central role played by the lungs in the onset and progression of RA. In particular interstitial lung disease (ILD) is a common pulmonary manifestation that may be related to the inflammatory process itself, infectious complications and to the treatments used. Management of patients with ILD/RA is still a challenge for clinicians, both synthetic [mainly methotrexate (MTX), leflunomide] and biologic immunosuppressors [mainly anti-tumor necrosis factor (TNF) α] have in fact been related to the onset or worsening of lung diseases with conflicting data. Here we report the case of a 61-year-old male patient with severely active early RA, previously treated with MTX, who developed subacute ILD, along with a review of ILD/RA topic. Tocilizumab (humanized monoclonal antibody against the interleukin-6 receptor) was introduced on the basis of its effectiveness in RA without concomitant MTX and the ability to overcome the profibrotic effects of interleukin (IL)-6. After 3 months of treatment the clinical condition of the patient strongly improved until it reached low disease activity. He no longer complained of cough and dyspnea and bilateral basal crackles were no more present. Considering its distinctive features, tocilizumab, in such a challenging clinical condition, appears to be a safe and effective therapy, thus it enables RA remission without deteriorating ILD, at 1-year follow up, as confirmed by ultrasonography of the affected joints and chest high-resolution computed tomography (HRCT).

Keywords: anti-TNF α agents, interstitial lung disease, rheumatoid arthritis, tocilizumab

Introduction

Rheumatoid arthritis (RA) is an inflammatory chronic autoimmune disease generally characterized by a progressive and disabling symmetric polyarthritis accompanied by specific autoantibodies. RA can also present different extrarticular manifestations involving heart, lungs and kidneys [Hallowell and Horton, 2014]. Even though the majority of RA-related deaths are linked to cardiovascular disease, pulmonary complications are common and cause 10–20% of overall mortality [Maradit-Kremers *et al.* 2005].

In particular interstitial lung disease (ILD) is a common pulmonary manifestation that may be related to the inflammatory process itself, infectious complications and to the treatments used. Both synthetic and biologic immunosuppressive agents have been related to the onset or worsening of ILD, making the adoption of safe and effective therapeutic approach difficult. Here we report the case of a 61-year-old male patient with early RA who developed subacute ILD under methotrexate (MTX) therapy, in which tocilizumab (humanized monoclonal antibody against

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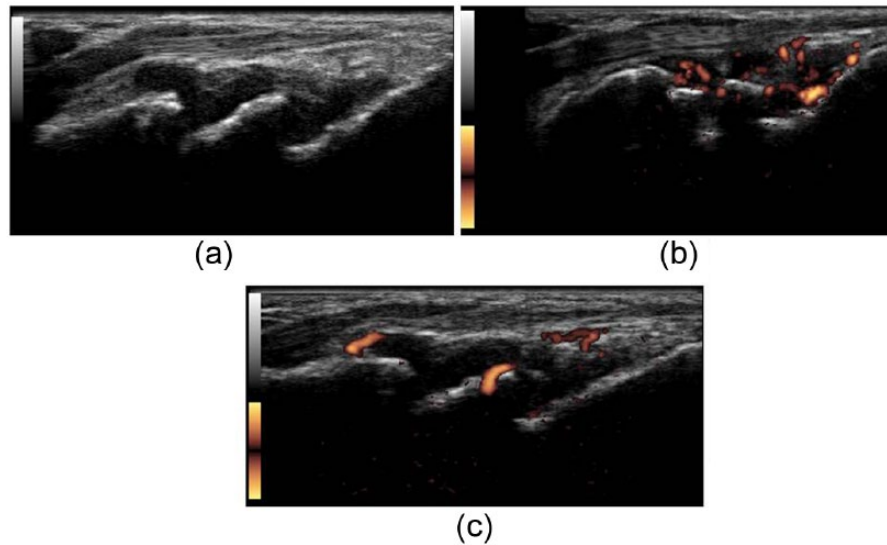


Figure 1. Ultrasonography of the right radiocarpal joint, longitudinal scanning. (a, b) Baseline: moderate synovial hypertrophy with severe activity (power Doppler III). (c) Three months follow up: mild synovial hypertrophy with mild activity (power Doppler I).

the interleukin-6 receptor) enables RA remission without deteriorating ILD.

Case report

In April 2013, a 61-year-old man suffering from early RA [2–10 small joints, increased erythrocyte sedimentation rate (ESR)/C-reactive protein (CRP), positivity of anticyclic citrullinated peptide antibodies (ACPA)/rheumatoid factor (RF), symptoms lasting 1 year] came to our attention for the worsening of morning stiffness, pain and symmetrical swelling of proximal interphalangeal (PIP), metacarpophalangeal (MCP) joints and wrists.

The patient presented several comorbidities: high blood pressure, type 2 diabetes mellitus, dyslipidemia, class I obesity [body mass index (BMI) = 33.2], prostatic enlargement and depressive mood. In addition, he was a smoker [60 pack-years (PY)].

He was receiving treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids (CCS) in the medium/high doses (up to 15 mg/day prednisone). During the first visit at our division, the patient exhibited laboratory investigation that showed ESR 37 mm/h, CRP 10 mg/l, RF 122 IU/ml, ACPAs 233 IU/ml; quantiferon-TB gold test, antinuclear antibody (ANA) and extractable nuclear antigen (ENA) screening

as well as complete hepatitis B and C markers were negative; blood count [white blood cells (WBC) $6.5 \times 10^3/\mu\text{l}$, granulocytes 55%, lymphocytes 35%], transaminases, creatinine and serum protein electrophoresis were normal. He did not present other clinical signs and symptoms suggestive of connective tissue disorders such as: Raynaud's phenomenon, skin thickening, dysphagia and acid reflux, rashes, sicca syndrome, myalgia and proximal muscle weakness, nor constitutional symptoms of fever and sweats. X-ray of November 2012 documented a mild increase of the plot in the absence of clinical signs; hands and wrists X-ray reported diffuse arthropathic manifestations with initial erosions of ulnar styloid. Ultrasound of hands and wrists bilaterally demonstrated moderate proliferative, erosive and active synovitis [power Doppler (PD) III] of radiocarpal joints, moderate active (PD II) proliferative tenosynovitis of the flexor tendons of the fingers, mild proliferative synovitis of the II MCP joint (Figure 1(a,b)). On examination, he presented four tender and four swollen joints (radiocarpal and II MCP joints bilaterally). Clinimetric data showed moderate activity with disease activity score in 28 Joints (DAS28) of 4.8 and moderate disability with Health Assessment Questionnaire (HAQ) of 1.5. We also performed the Short Form Questionnaire for general well being (SF-36) to gain a deep insight of his mental and physical quality of life. He presented a severe reduction (>2 standard deviations from the

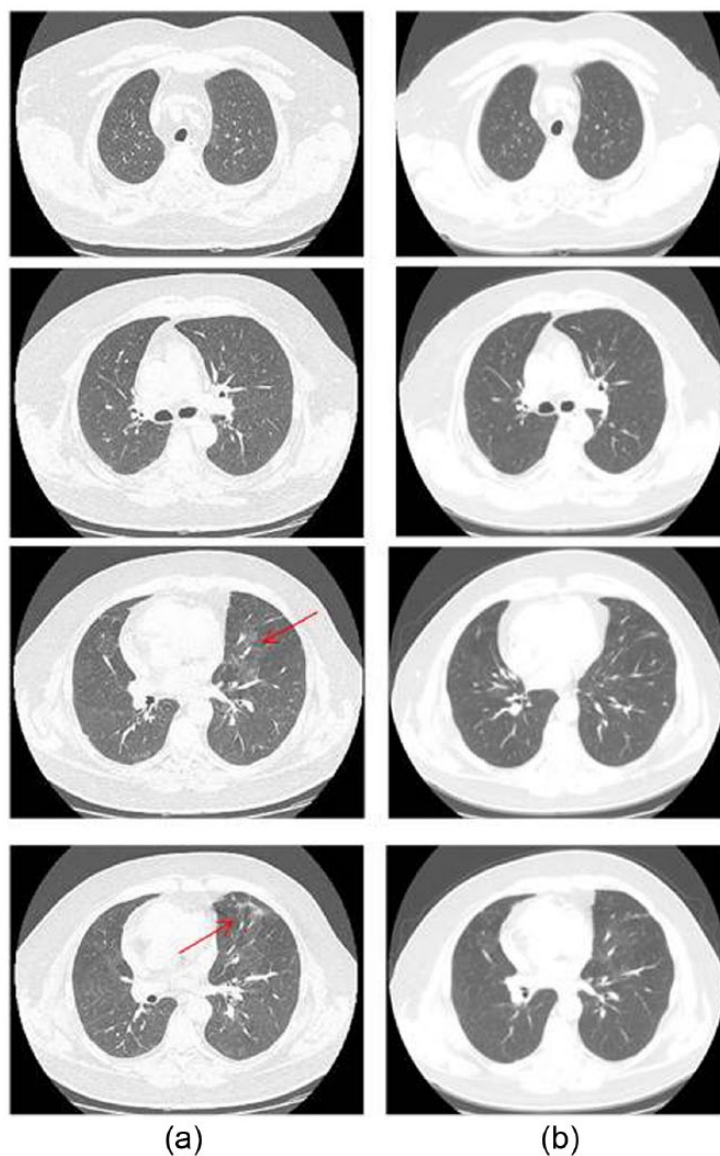


Figure 2. Chest high resolution computed tomography representative lung layers. (a) Baseline: inflammatory interstitial thickening with ground glass pattern (red arrows). (b) One-year follow up: reduction in size and density of the ground glass pattern.

mean) in all the SF-36 subscales with a Physical Component Summary (PCS) of 22 and a Mental Component Summary (MCS) of 26.

MTX 15 mg/week was, therefore, introduced and progressive CCS decrease (up to 5 mg/day) started. After 2 months of therapy with MTX, the patient showed significant improvement of RA signs and symptoms. However, he began to complain of persistent dry cough and dyspnea without fever. The objective examination of the chest documented bilateral basal crackles. In suspicion of ILD, the patient was submitted to lung function

tests that documented mild restrictive defect with mild reduction of CO single-breath diffusing capacity (DLCO SB 60%) and CO divided by the alveolar volume (DLCO/VA 87%; forced vital capacity 67%). High-resolution computed tomography (HRCT) showed one micronodule (5 mm) with smooth margins in subpleural parenchymal right upper lobe and notes of bilateral interstitial fibrotic *striae* type 'ground glass' more evident on the left (Figure 2(a)). MTX was interrupted and therapy with Sulphasalazine 2 g/day was introduced. The consultant pneumologist proposed to also perform a bronchoalveolar lavage (BAL)

which excluded concomitant infections and showed an increased cellularity with raised granulocytes (10%) and lymphocytes (20%), eosinophils and macrophages were within the normal range; the CD4/CD8 ratio was 1.3. The CCS dose was not increased; however, after 3 months the patient presented marked arthritic worsening with six tender and six swollen joints and a DAS28 of 5.8 (severe activity), accompanied by a deterioration of its depressive mood. Consequently, treatment with tocilizumab at recommended standard dose (8 mg/kg, total 760 mg ev/monthly) was introduced. After 3 months of treatment with tocilizumab, the clinical condition of the patient visibly improved. The clinimetric data showed low disease activity (DAS28=3) and a reduced disability (HAQ=1) confirmed by the marked amelioration in all the SF-36 subscales (PCS from 22 to 33 and MCS from 26 to 43). The patient presented only one tender and swollen joint (left radiocarpic joint). Ultrasonography of hands and wrists documented a mild synovitis (PD grade I) of radiocarpic joints bilaterally (Figure 1(c)). He no longer complained of cough and dyspnea and bilateral basal crackles were no more present. After 6 months of therapy with tocilizumab, the clinical conditions of the patient were still stable (DAS28=3); the tests of lung function showed persistence of mild restrictive defect with normal CO diffusion (DLCO/VA 102%).

At 1-year follow up the patient showed a clinical remission (DAS28=2), further improvement in disability (HAQ=0.5) and SF-36 (PCS 35; MCS 45). The objective examination of the chest was normal and the tests of lung function were stable. HRCT was repeated and it documented the reduction in size and density of ground glass area (Figure 2).

Informed consent was obtained from the patient for his information and images to be included in this article, as well as for diagnostic and therapeutic interventions. Our institution does not require ethics approval for reporting individual cases.

Discussion

In the patient here described tocilizumab was introduced on the basis of its distinctive features, such as the effectiveness in RA without concomitant MTX and the ability to overcome the profibrotic effects of IL-6. Moreover, the biological drug could safely be administered, since the BAL

had enabled to exclude pulmonary infections before the start of therapy. To the best of the authors' knowledge, this is the second case in the literature reporting tocilizumab as a possible treatment in this clinical condition.

ILD is a common pulmonary manifestation of RA that may be related to the chronic inflammation of the underlying disease, to infectious complications and to the treatments used [Hamblin and Horton, 2011]. The prevalence of clinical ILD in patients with RA has been reported by several authors in the wide range of 10–60% [Bongartz *et al.* 2010]. This variability may be related to lack of standardized screening protocols, including functional respiratory tests before starting immunosuppressive therapy. This may even condition the possibility of establishing a certain cause-effect relationship between drug assumption and ILD appearance/worsening. A further bias is the different sensitivity of the used diagnostic technique. In fact, it has been described in up to 80% of biopsies, 50% of chest CT and only 5% of chest X-ray [Crestani, 2005]. Mean age at the onset of lung disease is the fifth or sixth decade, with an increased prevalence in males and long-standing RA [Bilgici *et al.* 2005; Gochuico *et al.* 2008]. Smokers and patients with rheumatoid nodules, high titer of RF, ANA, ACPA, carriage of HLA-DRB1*1502 are described to be at higher risk of developing ILD, whereas disease severity seems to be an irrelevant factor [Lamblin *et al.* 2001; Mori *et al.* 2012]. Of note, the patient here described presented several of the among reported risk factors such as the RF, ACPA positivity and smoking.

Several histopathological patterns of ILD have been described: usual interstitial pneumonia (UIP) is the most frequent, followed by nonspecific interstitial pneumonia (NSIP); other patterns are less commonly observed [Koduri *et al.* 2010]. The incidence of ILD in RA patients is not only related to the disease itself, in fact many drugs may be associated with the development or worsening of pulmonary damage [Picchianti Diamanti *et al.* 2011]. The link between MTX and lung disease in RA patients has been recognized since many years and several reports have described induction or worsening of pneumonitis in a range of 0.86–6.9% of patients, with morbidity and mortality rates reaching 20% [Saravanan and Kelly, 2006]. Lung involvement may develop at any time during treatment, nevertheless it has

been described to manifest in 48% of affected patients within 32 weeks since the MTX introduction [D'Elia, 2014]. To distinguish between MTX-induced pneumonitis and RA-related ILD is crucial considering that the former can resolve with stopping MTX and continuing steroids whereas the latter needs specific treatment. Unfortunately to obtain a differential diagnosis remains a clinical challenge. In fact, MTX-related pneumonitis usually present more acutely than RA-associated ILD but the other clinical, imaging and histopathological features (i.e. dyspnea, nonproductive cough, ground glass opacities, lymphocytic alveolitis) are shared, thus rendering them sometimes indistinguishable [Saravanan and Kelly, 2004; Wells and Hirani, 2008]. An effective role in the differential diagnosis cannot be attributed either to the BAL cytological analysis. In fact it can show moderate lymphocytosis and high CD4/CD8 ratio [Fuhrman *et al.* 2001; Schnabel *et al.* 1997] in the MTX pneumonitis but these findings are nonspecific [D'Elia, 2014; Jakubovic *et al.* 2013]. According to the commonly accepted criteria for the diagnosis of MTX-induced pneumonitis, the case here presented can be interpreted as a probable, but not definite, case of MTX-related pneumonitis, only fulfilling five available (subacute onset dyspnea, dry cough, WBC less than 15×10^9 , negative blood and BAL cultures, restrictive defect and diffusion capacity on pulmonary function test) criteria [Searles and McKendry 1987].

Furthermore, considering all of the clinical, laboratory and imaging features, an underlying RA-related ILD cannot be excluded.

Current guidelines of the British Society for Rheumatology for the management of patients with RA have proposed to perform pulmonary function tests as a screening procedure before starting MTX thus helping to identify occult lung disease [Chakravarty *et al.* 2008]. Despite the association between pneumonitis and MTX is generally accepted, the ILD/MTX link is not clearly demonstrated and has been questioned by other authors. Dawson and colleagues [Dawson *et al.* 2002] performed chest HRCT and pulmonary function test in 128 RA patients and found no differences in the dose or duration of MTX therapy in the 28 patients presenting pulmonary fibrosis, suggesting no evidence of MTX-related chronic ILD.

Finally, a recent meta-analysis of Conway and colleagues [Conway *et al.* 2014] have demonstrated a mild increased risk of respiratory adverse events in patients with RA treated with MTX compared with other disease-modifying antirheumatic drugs (DMARDs) and biologic agents, however not higher increased risk of death. Leflunomide is also associated to ILD in RA patients, with higher risk in pre-existing lung disease and a potential relevant impact on survival [Raj and Nugent, 2013; Sawada *et al.* 2009]; few data are available regarding other synthetic DMARDs [Roubille and Haraoui, 2014].

Biological agents are nowadays considered the most effective therapeutic option in RA, especially when used in patients with early onset disease or poor prognostic factors, such as high titers of autoantibodies and high disease activity as in the patient here described [Smolen *et al.* 2010]. However, these drugs are not free from side effects. A possible correlation with RA-ILD has in fact been reported for several biologicals. In particular, new-onset or exacerbation of ILD after administration of all anti-tumor necrosis factor alpha (anti-TNF α) agents approved for the treatment of RA (infliximab, etanercept, adalimumab, certolizumab and golimumab) have been described by a number of reports and registry data, suggesting a class effect, rather than drug adverse event [Dixon *et al.* 2010; Hadjinicolaou *et al.* 2011; Kremer *et al.* 1997; Koike *et al.* 2011; Panopoulos and Sfikakis, 2011; Pearce *et al.* 2012; Perez-Alvarez *et al.* 2011; Schuller *et al.* 2010; Takeuchi *et al.* 2008]. Perez-Alvarez and colleagues [Perez-Alvarez *et al.* 2011] identified 122 cases (108 RA) of new onset or exacerbation of ILD secondary to administration of biologic therapies (58 etanercept, 56 infliximab, 3 adalimumab and 5 rituximab). The poor prognosis was associated with age >65 years, late onset of symptoms, frequent use of other immunosuppressants (especially MTX), and a previous diagnosis of ILD [Perez-Alvarez *et al.* 2011].

A review by Panopoulos and Sfikakis [Panopoulos and Sfikakis, 2011] reported 144 cases of new onset (60%) or exacerbation of preexisting ILD (40%) in RA patients following anti-TNF α treatment (55 infliximab, 95 etanercept, and 4 adalimumab). Nakashita and colleagues retrospectively analyzed 163 patients with RA treated with biological agents (63 etanercept, 33 infliximab, 6 adalimumab, 36 tocilizumab, 25 abatacept) and

observed a prevalence of 3% of new ILD events and 24% of ILD worsening with the use of TNF α agents [higher than previously reported (0.5–0.6%) from post-marketing data surveillance] [Koike *et al.* 2011; Takeuchi *et al.* 2008], whereas tocilizumab and abatacept did not increase the prevalence of ILD events [Nakashita *et al.* 2014].

Despite the previously mentioned evidence, the association of anti-TNF α treatment and ILD has been recently questioned. As a matter of fact, a retrospective study including 8417 patients affected by RA, ankylosing spondylitis, psoriatic arthritis, psoriasis and inflammatory bowel disease did not present an increased rate of ILD compared with those treated with nonbiologic drugs [adjusted hazard ratio, 1.03; 95% confidence interval (CI) 0.51–2.07]; with not significant differences among anti-TNF α molecules [Herrinton *et al.* 2013]. In addition, in sporadic cases good results have been reported by the use of these agents in patients with RA-ILD [Bargagli *et al.* 2004; Vassallo *et al.* 2002]. These conflicting results may be explained by the complex and pleomorphic activity of TNF α and reflect the need to elucidate the relationship between anti-TNF α agents and ILD. Different studies on animal models have in fact demonstrated a profibrotic role for this molecule. Transgenic mice overexpressing murine TNF α in the lung develop a chronic lymphocytic alveolitis, the severity of which correlates with the expression of TNF α mRNA. Moreover, TNF α may upregulate TGF β 1 expression in the lungs via the activation of regulated kinase pathway in fibroblasts [Miyazaki *et al.* 1995; Sullivan *et al.* 2009]. Otherwise, mice knockout for TNF α develop a bleomycin-induced lung fibrosis that may be reverted by the administration of TNF α [Kuroki *et al.* 2003]; TNF α is also able to block the synthesis of collagen production and inhibits α 2 collagen gene transcription in human dermal fibroblasts [Kouba *et al.* 1999].

Few reports of ILD onset/worsening are also present in the literature in patients receiving rituximab and abatacept therapy [Soubrier *et al.* 2008; Wada *et al.* 2012; Wagner *et al.* 2007].

Improvement of RA-ILD with tocilizumab has been observed in a single case report [Mohr and Jacobi, 2011]. The case of 58-year-old female patient with seropositive RA treated with MTX

until she developed MTX-related ILD has been reported. The tests of lung function documented mild reduction of CO and HRCT evidenced alveolitis. Thereafter, treatment with tocilizumab was started as monotherapy. Within 16 weeks, the patient presented an improvement in the diffusion of CO, absence of dyspnea and improvement in RA disease activity. A 6-month follow-up HRCT documented disappearance of ground glass infiltrates and lack of fibrotic reorganization of the lung tissue [Mohr and Jacobi, 2011]. In contrast, other authors addressed ILD occurrence or exacerbation following tocilizumab therapy [Kawashiri *et al.* 2012; Wendling *et al.* 2013].

Conclusion

Therapeutic management of patients with ILD associated with RA is still a challenge for clinicians. In fact, most drugs used for RA treatment have been reported to be related with onset or worsening of ILD. Several reports suggest also a causative role for TNF α inhibitors in RA-ILD development/worsening; however, no definitive conclusion can be drawn hence data are conflicting and affected by several variables. Current knowledge on the role of biologics with different mechanism of action is limited. In this context, tocilizumab appears as a therapeutic strategy based on a solid rationale, considering that it can overcome the profibrotic effects of IL-6 and it is the only biologic equally effective in RA, even in the absence of concomitant MTX. Here the case of a 61-year-old male patient with early RA, previously treated with MTX who developed subacute ILD is reported. Our investigations did not confidently distinguish between MTX pneumonitis and RA related ILD; however, in such a challenging clinical condition, tocilizumab appears to be a safe and effective therapy, thus it enables RA remission without deteriorating ILD, at 1-year follow up, as confirmed by ultrasonography of the affected joints and chest HRCT.

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Conflict of interest statement

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