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Case report

Janus kinase inhibitors as a therapeutic option in rheumatoid arthritis and associated interstitial lung disease. Report of four cases☆

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ABSTRACT

Rheumatoid arthritis (RA) is a systemic disease for which multiple therapeutic options have been developed in the last decades. Based on the information available in the literature, the use of biological therapy in patients with diffuse lung disease is not recommended because these medications can exacerbate the lung disease. A newer drug is the Janus kinase enzyme inhibitor, which can be used as monotherapy or in combination in patients with moderate to high activity RA, in whom the use of synthetic or biological DMARDs is contraindicated, as well as in patients with therapeutic failure. However, the pulmonary safety of the drug has not been evaluated in clinical trials and the information available is limited. This article discusses the treatment, follow-up, and outcomes of the use of tofacitinib in a series of 4 patients with lung disease secondary to RA.

Inhibidor de Janus quinasas como opción terapéutica en artritis reumatoide y enfermedad pulmonar intersticial asociada: reporte de 4 casos

Palabras clave:
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Enfermedades pulmonares intersticiales
Inhibidor de quinasas Janus
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RESUMEN

La artritis reumatoide (AR) es una enfermedad sistémica que en las últimas décadas ha tenido múltiples opciones terapéuticas. Con la información disponible en la literatura no se recomienda el uso de terapia biológica en pacientes con enfermedad pulmonar difusa, dado que estos medicamentos pueden exacerbar el compromiso pulmonar. Un medicamento de más reciente aparición es el inhibidor de la enzima Janus quinasa, el cual es una opción

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terapéutica en monoterapia o combinado para pacientes con AR en moderada y alta actividad de la enfermedad, con contraindicación al uso de FARME sintéticos o biológicos, y en pacientes con fallo terapéutico, no obstante, su seguridad a nivel pulmonar no ha sido evaluada en ensayos clínicos y la información disponible es escasa. Describimos el tratamiento, seguimiento y resultados del uso de tofacitinib en 4 pacientes con enfermedad pulmonar secundaria a AR en una serie de casos.

Introduction

Rheumatoid arthritis (RA) is an autoimmune disease, characterized by chronic joint inflammation, but it is also considered a systemic syndrome including extra-articular manifestations, such as rheumatoid nodules, vasculitis, pulmonary and cardiovascular involvement, among other comorbidities.[1]

The lung involvement in the patient of RA is diverse, including parenchymal disease (interstitial lung disease (ILD)), pleural inflammation (pleural thickening and effusion), pulmonary airway and vasculature (vasculitis and pulmonary hypertension).[2]

There has been a transformation in the treatment of RA over the last few years, due to the emergence of biologicals that reduce the progression of the disease and significantly improve the joint symptoms, function and quality of life.[3] Biologicals are recommended by the major management guidelines for patients with persistent symptoms that fail to respond to synthetic disease modifying anti-rheumatic drugs (DMARDs).[4,5] However, several cases published have associated various DMARDs – methotrexate in particular – and biological therapy with exacerbation and severe adverse respiratory events,[6] that develop as a result of different mechanisms, including the induction of idiosyncratic reactions secondary to medication, modification and acceleration of a pre-existing ILD, a more aggressive phenotype, and increased susceptibility to infections.[7] Consequently, the safety of biological therapy and of some DMARDs in patients with RA-associated ILD (AR-ILD) is actually uncertain, and this fact has led to an increased use of corticosteroids and immunosuppressive medications such as azathioprine or mycophenolate mofetil in these patients, to avoid undesirable pulmonary adverse effects. A more recent drug is the Janus kinase enzyme inhibitor (tofacitinib), which represents a treatment option as monotherapy or in combination for patients with moderate to high activity RA, and in whom synthetic or biological DMARDs are contraindicated, and in patients that have failed therapy[4,5]; however, the pulmonary safety of the drug has not been evaluated in clinical trials and the information available is limited.

This article describes the treatment, follow-up and results of the use of tofacinitib in a series of 4 patients with lung disease secondary to RA.

Case 1. 80-year-old female patient with a history of RA with 11 years of evolution, that failed hydroxychloroquine and methotrexate (MTX) therapy, and is undergoing treatment with leflunomide, sulfazalazine, and prednisone, but the disease is not properly controlled. The patient was hospitalized with arthritis in the elbows, wrists, metacarpophalangeal (MCP) and proximal interphalangic (PIP) joints, the knees and the ankles (bilateral), associated with dyspnea on mild exertion. Rheumatoid factor (RF): 512, anti-citrulline antibodies (anti-CCP): >200, CRP: 31, ESR: 117, chest-CT: interstitial pneumonia with a non-specific interstitial pneumonia pattern, and bilateral pleural effusion. DAD-28-CRP: 6.46, DAS-28-ESR: 7.6. A pulse therapy protocol for RA-associated interstitial pneumonia was administered. Leflunomide was discontinued due to lung toxicity and the use of anti-TNF was ruled out since it is contraindicated in case of lung disease exacerbation. The patient was treated with tofacitinib 10 mg/day after screening for hepatitis B, C and latent TB. The clinical condition and the laboratory parameters improved with low disease activity, with no pulmonary exacerbation after 12 months of follow-up and no re-admissions.

Case 2. 78-year-old male patient with RA for 15 years, treated with hydroxychloroquine, sulfasalazine, with no adequate control of the disease. MTX and leflunomide were discontinued due to interstitial lung disease with a usual interstitial pneumonia pattern, chronic use of prednisone. MCP and PIP arthritis, knees, associated with dyspnea on mild exertion. RF: 64, anti-CCP: >200, CRP: 25, ESR: 48, DAS-28-CRP: 5.7, DAS-28-ESR: 6.4. The patient received methylprednisolone pulses and then tofacitinib 10 mg/day, with improved clinical condition, with no pulmonary exacerbations after 8 months of follow-up, with no readmissions.

Case 3. 83-year-old female patient, with a history of liver cirrhosis. Chronic obstructive pulmonary disease (COPD) Gold C, non-specific pattern interstitial pneumonia, RA treated with hydroxychloroquine and prednisone. MTX and leflunomide were discontinued due to liver cirrhosis. Symmetrical arthritis in hands and knees. RF: 8.0, anti-CCP: 8.8, CRP: 23, ESR: 34, DAS-28-ESR: 5.1, DAS-28-ESR: 5.7. The patient received methylprednisolone pulses, tofacitinib 10 mg/day, with improved clinical condition, with no pulmonary exacerbation after 10 months of follow-up and no hospital readmissions.

Discussion

The primary objective of managing RA patients is to control inflammation, preventing joint damage, and improving physical function.[1] The treatment requires a step-wise approach consistent with the level of activity of the disease, starting with DMARDs that are the cornerstone of drug therapy;

nevertheless, when patients fail to respond to the first-line therapy, they are switched to biologicals.[1,4,5] However, the use of biologics may be difficult in patients with RA-associated interstitial lung disease, because of the risk of exacerbation and accelerated disease progression.[6,7] This concern developed following the publication of more than 100 cases of the fatal exacerbations due to RA-ILD upon the introduction of the first anti-TNF agents,[8] and this has also been the case with the newest anti-TNF drugs.[9–11]

Whilst the data are insufficient to differentiate the safety profiles of the various drugs used in RA, the use of anti-TNF agents is not safe, particularly in patients with pre-existing ILD; however, these patients have been excluded from the trials and hence, the information about exacerbations has not been assessed.[12]

The selective inhibitor of the intracellular Janus kinase molecule (tofacitinib) has been indicated for patients with active RA and who failed DMARD therapy or treatment with other anti-TNF agents; tofacitinib may be used as monotherapy or combined therapy to control the disease.[4,5] This drug is considered a synthetic DMARD, notwithstanding the fact that it interferes with a biological pathway one level above that of some of the available biologics.[13] There have been no case reports of exacerbation or severe respiratory events secondary to tofacitinib to this date. In a phase III trial of this agent in combination with methotrexate conducted in 717 patients, of which 513 received tofacitinib, 2 new cases of ILD and one case of pulmonary sarcoidosis were reported after one-year follow-up.[14] Another trial reported 3 cases of COPD, one of them associated with ILD using tofacitinib as monotherapy, among 611 patients followed for 6 months.[15] It is however difficult to establish treatment causality and to this date there are no clinical trials evaluating the safety of the JAK inhibitor in patients with RA-ILD. Although pulmonary complications were only described in less than 1% of the patients participating in the above-mentioned trials, its use has been restricted probably upon extrapolating the data from publications on other DMARDs and anti-TNF agents.

Considering the limited information available, a series of 4 cases of patients with RA and pre-existing ILD, with moderate/high disease activity in whom treatment goals with DMARDs were not attained and led to the initiation of tofacitinib administration, either alone or in combination is herein reported. During the follow-up period (between 8 and 12 months) there were no exacerbations of the interstitial disease. This description is important because this is the first report on the use of Janus kinase inhibitors in patients with pre-existing ILD, with no evidence of exacerbation of their pulmonary condition, with a follow-up period of up to one year and clear indication to control the activity of the disease.

In conclusion, although the Janus kinase inhibitors are not the standard for the management of patients with RA-ILD, our experience has been encouraging. However, further studies are needed to orient treatment for this group of patients in the future.

Conflict of interest

There is no conflict of interests to disclose.

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