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Mini Review: Pulmonary Toxicity Secondary to Immunosuppressive Agents in the Treatment of Rheumatoid Arthritis

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1. Abstract

Rheumatoid arthritis (RA) is a chronic rheumatic disease, characterized by erosive and destructive arthritis, representing an important cause of disability. Interstitial lung disease is not a rare event and can be aggravated by several immunosuppressive medications. Methotrexate, once seen as a drug associated with interstitial pneumonitis, is now seen as an agent capable of slowing or preventing the progression of lung disease related to rheumatoid arthritis. Anti-TNFs currently represent the class with the greatest impact on the course of pulmonary disease in RA, with a significant increase in mortality. Among the immunobiological agents, abatacept and Rituximab stand out in relation to the pulmonary safety profile.

2. Introduction

Rheumatoid arthritis (RA) is a chronic rheumatic disease, of unknown etiology and essentially autoimmune in nature. It is characterized by chronic, erosive and destructive polyarthritis, affecting mainly small peripheral joints, representing an important cause of physical disability and disability [1]. In the last 20 years, profound changes in its therapy have occurred, especially with the popularization of immunobiological therapy and concepts that set strict therapeutic goals, aimed at achieving remission or low disease activity [2].

The advent of new options for disease-modifying drugs (DMARDs) has resulted not only in a better prognosis, but also in greater concern about possible adverse events. Historically, the increased risk of infections has always been recognized as the greatest challenge of immunosuppressive treatment. Today, however, a series of visceral damage is recognized, potentially associated with certain DMARDs, with pulmonary toxicity standing out among them [3].

Pulmonary complications occur in approximately 60 to 80% of patients with RA. A Brazilian study, evaluating RA patients with chest X-ray and spirometry, revealed changes in the respiratory system in 57.8% of individuals [4].

The risk of RA-associated interstitial pneumonitis is higher in individuals with positive rheumatoid and / or anti-CCP factors, with frequent observation of asymptomatic patients with subclinical disease. It usually occurs in the first five years of the disease and it may precede joint involvement in up to 20% of cases. Among the possible manifestations, interstitial lung disease stands out, notably the usual interstitial

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pneumopathy (PIU) and non-specific interstitial pneumonitis. Organized pneumonia, diffuse alveolar damage and lymphocytic interstitial pneumonia are also described [5].

Drug-induced lung disease is an important differential diagnosis in patients with RA and respiratory complaints. The DMARDs can trigger alveolar and / or interstitial inflammation, in addition to tissue fibrosis. The risk of toxicity is variable and depends on the class of medication used [5].

DMARDs generally have a beneficial impact on the course of RA, including the prevention and treatment of their pulmonary manifestations, reducing their occurrence by up to 50%. Although such a protective effect stands out, there are, on the other hand, consistent reports of pulmonary toxicity related to the use of several immunosuppressive agents in the course of RA treatment. Acute or subacute hypersensitivity reactions are described, resulting in pneumonitis, or the occurrence of medication-related pulmonary fibrosis, or even the acceleration of the progression of pre-existing interstitial pneumopathy, with a significant increase in mortality [6].

Acute interstitial pneumonitis that occurs in the context of hypersensitivity to the drug, is accompanied by dry cough, progressive dyspnea, low fever, erythematous, pruritic skin rash and the finding of crackling bibasal rales on respiratory auscultation is common.

It is necessarily a diagnosis of exclusion and the possibility of an infectious condition should always be excluded, especially bacterial pneumonias and the pulmonary manifestations of the disease itself. Complementary exams may show changes suggestive of this complication, such as peripheral blood eosinophilia, ground glass interstitial infiltrate on chest tomography and hypercellularity at the expense of eosinophils in bronchoalveolar lavage [7].

Next, we will present the main data on the relationship between drugs used in the treatment of RA and pulmonary involvement.

3. Synthetic Disease Modifying Drugs

Methotrexate, a drug considered the gold standard in the treatment of RA, has over time been implicated in the development of acute, subacute and chronic interstitial lung disease and also in the progression of subclinical pulmonary fibrosis related to the underlying disease [3].

In recent years, however, the role of this drug in the genesis of pulmonary changes has been reviewed, with recent evidence pointing to a protective role for this medication. Juge et al., evaluated 1083 RA patients and found previous pneumopathy in 673 patients. The authors concluded that methotrexate reduced the frequency of pulmonary manifestations and also the progression of pre-existing interstitial pneumonitis [8].

In patients with methotrexate intolerance or failure, leflunomide is an important alternative in the treatment of joint disease. Reports and case series correlate this medication with the appearance of pulmonary nodules and with pulmonary fibrosis [9]. The estimated risk of pneumopathy is relatively low, approximately 1.2%. The groups most vulnerable to this complication are individuals with previous interstitial lung disease and those with a history of hypersensitivity to methotrexate [9].

Target-specific disease course-modifying drugs (tofacitinib, baracitinib and upadacitinib) have recently been incorporated into the therapeutic arsenal in RA. They are important options both in the failure of synthetic and biological DMARDs [2].

Interstitial lung disease is rarely described with tofacitinib, almost always seen with concomitant use of methotrexate. The casuistry is still small with such medication, making it impossible to conduct a deeper analysis regarding its safety in individuals with pulmonary involvement. Rivera et al. reported a series of four cases of severe RA associated with chronic interstitial pneumonitis, where no signs of worsening of the previous pulmonary condition were observed with the use of tofacitinib [10].

4. Biological Disease Modifying Drugs

Immunobiological agents have revolutionized the treatment of rheumatoid arthritis, resulting in a significant impact on the control of pain, inflammation, prevention of joint damage, inhibition of disease progression and maintenance of patients' functional capacity [11]. They also reduced the frequency of visceral manifestations, including the occurrence of clinical interstitial lung disease [2].

The pulmonary toxicity of these medications is considered a rare event, occurring in less than 1% of cases. The real risk of this complication, however, is difficult to measure, as patients using these agents are, in general, considerably more severe and at higher risk of visceral manifestation related to the underlying disease [12].

Anti-TNFs seem to increase mortality from RA-related interstitial lung disease, when compared to other drugs, with a higher risk in the elderly. San Koo et al. observed a 25% mortality rate in patients with interstitial pneumopathy, using anti-TNF [13]. Data from the British Biological Registry point to a three-fold higher mortality rate in patients with RA and pneumopathy who regularly used these medications, when compared to the group that used other DMARDs [12].

Rituximab, an anti-CD 20 monoclonal antibody, reports on the occurrence of pulmonary fibrosis, especially in patients with lymphoma. In RA patients, this adverse reaction is rarely described. In their study, Yosuf et al., analyzing patients with RA and interstitial pneumopathy using rituximab, did not observe a clinical progression of pulmonary disease progression [14]. In a systematic review, Cassone et al. observed that 83% of patients with RA and interstitial lung disease showed improvement or stabilization of lung function, with the use of this immunobiological agent [15].

Tocilizumab, a monoclonal anti-IL-6 receptor antibody has been studied as an alternative in patients with RA and pulmonary manifestations. In a study with 28 patients, Manfredi et al. concluded that the drug was safe and effective in controlling the disease, both from a joint point of view and in stabilizing lung function [16].

In the systematic review, Cassone et al. observed improvement or stabilization of pulmonary function in most patients (83%) using this immunobiological product [15].

Abatacept, an inhibitor of T lymphocyte co-stimulation, has proven to be an important alternative in the treatment of the binomial AR / interstitial lung disease.

In the study by Fernandez-Diaz et al., Of a total of 63 patients, two-thirds had stabilized pulmonary function and a quarter of the patients evolved with an improvement in pulmonary function parameters [17]. Cassone et al. observed maintenance or improvement in lung function in 91% of patients using abatacept [15].

5. Conclusion

Drug-induced lung toxicity is a controversial subject in the literature.

The lack of prospective studies involving large populations and the absence of guidelines, hinder a standardized clinical approach both in the management of RA with subclinical lung disease and in patients with progressive interstitial pneumopathy. Further studies are needed to define consensual approaches for this subgroup of RA patients.

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