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TREATMENTS OF RHEUMATOID ARTHRITIS AND INTERSTITIAL LUNG DISEASE

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ABSTRACT

Rheumatoid arthritis (RA) is a systemic autoimmune disease affecting 0.5–1% of the worldwide population. Interstitial lung disease (ILD) is the most common respiratory manifestation of RA. It significantly affects the prognosis and limited treatment options for RA. With the current state of evidence, most treatments of RA are associated with a risk of onset or exacerbation of ILD, but with very different prevalence. However, methotrexate is associated with a risk of hypersensitivity pneumonitis, its link with a chronic ILD are unlikely. Cyclosporine appears effective and tolerated in ILD associated to other connective tissue diseases. Regarding biologic agents, rituximab remains relatively the best tolerated drug. Moreover, it is difficult to differentiate drug-induced toxicity from ILD related to rheumatoid arthritis or infections. In practice, the occurrence of ILD in RA requires an etiologic screening and pulmonary function tests. The decision to start cDMARDs or a biologic agent in patients at risk for ILD should be based only on its potential for improvement, especially in the absence of an alternative drug, with close monitoring and an extensive explanation to the patient.

KEYWORDS: Interstitial lung disease; Rheumatoid arthritis; therapy.

INTRODUCTION

Rheumatoid arthritis (RA) is the most common chronic inflammatory disease, it affects 0.5% to 1% of the world's population.[1] Interstitial lung disease (ILD) associated with RA is the most common respiratory event and could affect one in four patients during the evolution, but often remains asymptomatic.[2]

The ILD could be specific to RA, to infectious complications, or drud induced. In all these situations it is associated with higher morbidity and mortality[3], also it limits therapeutic possibilities of RA. The purpose of this article is to review recent data from clinical research on the different classical and biological treatments of the PR and their links with ILD.

C- DMARD

methotrexate

Methotrexate (MTX) is discovered in 1948.[4] It is an immunosuppressive treatment which acts by competitive inhibition of dihydrofolate reductase (key enzyme in the synthesis of purine bases and pyrimidics). DNA synthesis is blocked inducing cellular apoptosis.[5] Although the MTX constitutes the gold standard in the treatment of RA, its mechanism of action remains unclear. Initially, the most admitted theory was an antiproliferative action on immune cells.[6] Later, Mr. Cronstein demonstrated on experimental models that the anti-inflammatory activity of MTX was related to stimulation of the secretion of adenosine (endogenous mediator involved in regulating inflammatory responses), wich allows inhibition of the immune cells mainly neutrophils.[7]

The link between MTX and ILD during RA is relatively difficult to prove. Some studies (on experimental models), have shown that MTX administered systemically increases the secretion of adenosine which could promote the production of collagen and the fibrotic process.[8] Recently, Chunn JL et al. have highlighted, still on experimental models, that increased secretion of adenosine could promote the proliferation of fibroblasts via the effect of some pro-fibrotic cytokines such as IL-1b and IL13, with some reversibility of the process after renormalization of the adenosine level.[9]

MTX can cause an acute or subacute interstitial lung disease, the incidence does not exceed 0.3% patient-year. It's an immunoallergic complication happening frequently during the first months of treatment. It is favored by the pre-existence of pulmonary involvement, advanced age, diabetes, hypoalbuminemia and high dose use MTX. It is manifested by quickly progressive

dyspnea, dry cough, fever, or by a table of acute respiratory failure. The chest scanner allows to show localized or diffuse lesion with sometimes a reticular and nodular appearance. The occurrence of this serious complication, fortunately very rare, imposes the immediate stop and very often definitive of MTX.[10,11]

The concept of a probable chronic ILD secondary to MTX is still debated. Initially, some clinical trials evaluating lung function under MTX, have incriminated this drug in the occurrence of several respiratory complications including PID. Indeed, this work presented inconclusive results because of many biases especially the limited number of patients and the absence of a control group.[12]

A prospective observational study including 128 RA patients, randomized into 2 arms and followed for 2 years (55 patients treated with MTX alone, and 73 patients with other c-DMARD) did not show any difference in pulmonary toxicity between the two groups. At the inclusion, the average age of the patients was about 60 years, with active smoking in 20% of patients, but without significant difference in lung functions between both groups. After two years of follow-up, 28 patients presented an ILD at the chest scanner (11/55 under MTX and 17/73 under other treatments), but there was no significant difference between the 2 groups, at the level of the functions and at the CT scan.[13] In 2014, R. Conway et al. performed a meta-analysis including 22 randomized controlled trials of 8584 RA patients: 4544 under MTX and 4040 under another c-DMARD. The authors are shown through this meta-analysis that there was no association between the use of MTX and the occurrence of an Noninfectious Respiratory event including ILD (RR 1.02, IC 95%: 0.65-1.60).[14] More recently, the same author conducted a literature review with meta-analysis including seven studies, and 1640 patients followed for psoriasis, psoriatic arthritis, and chronic bowel inflammatory diseases: 818 treated with MTX and 812 by another treatment. It is well known that the occurrence of a ILD associated with these pathologies remains unusual. The analysis of the results of this study did not allowed to show a significant difference between the two groups in the probability of occurrence of different respiratory events. Moreover, there was no deterioration of lung function in MTX patients compared to the other group.[15] This study has probably limited power given certain biases[16], but it seems that there is no argument to support the hypothesis that MTX causes chronic ILD. More controlled trials must therefore be conducted to determine whether there is a relationship between the use of MTX and the occurrence of ILD.

Leflunomide

Leflunomide (LFN) is an original immunomodulator which acts by competitive inhibition of dihydro-rotated dehydrogenase;(a key enzyme in the synthesis of novo pyrimidine bases); It slows the proliferation of immune cells especially activated T cells involved in the physiopathology of RA. For the past ten years the LFN has been one of the main treatments of RA. It's used as an alternative to MTX and its effectiveness appears comparable to this one.[17] The LFN can be associated with the onset or exacerbation of PID in 1.2% of treated patients.[18]

The pulmonary effects appears in the first weeks of treatment and can be present in the form of ILD, an organized pneumonia or more rarely in the form of diffuse alveolar damage.[19] A recent meta-analysis including 8 controlled randomized studies revealed that LFN is associated with a higher risk of non-infectious respiratory complications including ILD (RR 0.64, 95% CI 0.41- 0.97).[20] Indeed, ILD's linked to LFN are rare in Europe (<1%), but more common in Japan (0.5%). In 2013, Raj et al. identified 42 cases, of which 38% patients developed acute respiratory failure (IRA) with a mortality rate exceeding 20%.[21] The pathophysiological mechanism of these ILD remains unclear. These are likely hypersensitivity reactions happening more frequently during the first months of treatment. Risk factors are the administration a loading dose, smoking, a weight under 50 kg, hypoalbuminemia and a Pre-existing ILD.[10] We also note the genetic predisposition in some ethnic groups especially the Japanese and Korean.[22] It is clear that LFN is associated with serious ILD, and should be avoided in all patients with high risk. In case of ILD under LFN, it is necessary to stop immediately the treatment and carry out a wash-out by activated charcoal or cholestyramine.[21]

cyclosporine

Cyclosporin A (CsA); an immunosuppressive who acts by inhibition of T cell activation by calcineurin binding. The results of several studies have suggested that T cells are involved in the pathogenic mechanism of ILD associated with RA and could be a therapeutic targets[23] the effectiveness of CsA in the treatment of refractory RA has long been demonstrated[24], to the best of our knowledge there are no long-term studies showing the ratio efficacy / tolerance of this treatment in the associated ILD with RA. On the other hand, several studies have confirmed effectiveness in the treatment of ILD associated with others connectivites.[25] Moreover, a retrospective study including 26 patients followed for connective tissue disease ILD and treated with cyclosporine and corticosteroid low dose, showed a marked improvement in respiratory functions in all patients after one of monitoring. It is 12 PR, 4 systemic scleroderma, 7 dermatomyositis, 2 Sjögren-Gougerot, and a single case of Systemic lupus, The diagnosis of ILD has been confirmed by surgical biopsy, the patients were put under Cyclosporine 3mg / kg / day with corticosteroid therapy low dose and followed for one year with evaluation of respiratory functions at one month of treatment and then after a year. At the end of this study, the authors showed a significant improvement of respiratory functions at all patients.[26] It should be

noted that no case of ILD related to cyclosporine has not been reported in the literature.

BIOLOGICAL DMARD

Anti-TNF alpha

The anti-TNF alpha are the first line biological treatments of RA. They have demonstrated their effectiveness as well on the symptoms and on the RA structural progression. They are more and more incriminated in the ILD appearance or exacerbation. In a series of 226 patients (83% PR) treated with anti-TNF alpha, the authors observed that 10% of patients developed ILD.[22] In addition, one hundred and forty-four cases of ILD with anti-TNF alpha have been described in the literature and listed in the article by Panopoulos and Sfikakis. The most cases have been reported with Etanercept and Infliximab.[27] The overall incidence of ILD with anti-TNF varies between 0.5 and 0.6% and practically similar for all anti-TNFα (10). They are favored by the co-prescription of MTX and the preexistence of a ILD. However, a recent study including 8417 patients without pre-existing ILD, randomized in 2 arms (one arm under anti-TNF alpha and the other arm under c-DMARD) did not show any difference of ILD incidence between the anti-TNF alpha group (0.5%) and the group under other treatments (0.3%).[28] In addition, C.Roubille et al. reported a stabilization and an improvement in ILD of 5 patients treated with anti-TNF alpha.[10] The pathophysiological mechanism of ILD related to anti-TNF alpha remains unknown.

In the physiological state, TNF alpha is a pro-inflammatory cytokine of immune dsfense. Experimental studies have shown that may have a pro-fibotic or anti-fibrotic effect. On the one It can inhibit pulmonary fibrosis by decreasing inflammation via apoptosis of inflammatory cells and interaction with interleukin-1 and interferon-gamma. On the other hand, It's involved in the pathogenesis of pulmonary fibrosis by modulation of TGF beta and fibroblastic proliferation. Fibrosis biopsies of Idiopathic pulmonary disease demonstrated the presence of TNF alpha in macrophages and epithelial cells.[29] An imbalance of the balance between these two roles may induce ILD in some patients treated with anti-TNF alpha or, on the contrary, stabilize pre-existing ILD in others.[10] In practice, the occurrence of ILD under anti-TNF alpha requires immediate cessation of treatment and introduction of corticosteroids in high dose.

Rituximab

Rituximab is a chimeric monoclonal antibody directed against the CD20 antigen. It attacks B cells. Biopsies of ILD associated with RA have demonstrated the presence of follicular hyperplasia of B cells associated with interstitial infiltration, which assumes a role for these cells in the pathogenesis of ILD related to RA.[22] In the literature, one hundred twenty-one cases of toxicity have been reported during the use of RTX. Most patients had as an indication a malignant hemopathy and only 9 patients had systemic or autoimmune disease.[30] Indeed, ILD under RTX is very rare and does not exceed 0.03% (540,000 cases treated).[31] Recently, a randomized controlled trial evaluating efficacy and tolerance of RTX in 465 RA patients did not record any correlation with the occurrence of ILD.[32] Otherwise, some observational studies suggest an effect benefit of RTX on ILD associated with others connectivites especially systemic scleroderma and systemic lupus.[22] Two recent retrospective studies assessing RTX tolerance in patients PR with an associated ILD (n = 19 and n = 49 respectively) report a stabilization of the pulmonary involvement.[10] Waiting for other prospective clinical trials and multicenter studies evaluating the efficacy and tolerance of RTX in ILD associated with RA. Finally and according to the data of literature, RTX remains relatively well tolerated in associated ILD with RA.

Other biotherapies

Concerning tocilizumab (TCZ), Non-infectious pulmonary diseases were found in 6 patients (1%) out of a total of 589 RA patients treated by TCZ in 3 randomized controlled trials.[33] A case of fatal exacerbation of diffuse interstitial pneumopathy in the context of RA under TCZ a has been reported in the literature.[34] According to the japanese register experience, 23 patients had an exacerbation of ILD among 3881 RA patients including 13 patients with pre-existing ILD with incidence of 1.2% / year.[35]

Abatacept (ABA), a fusion protein, which inhibits the costimulatory signal required for activation T cells. Cases of exacerbation of chronic obstructive pulmonary disease have been described with this drug. Recently, Weinblatt et al conducted a meta-analysis including eight studies with 3171 patients followed for RA and treated by ABA and they reported 11 ILD case (0.3%) with an incidence of 0.11% / year.[36]

CONCLUSION

Pulmonary involvement during RA is common and dominated by ILDs. It is associated with an increased mortality and morbidity and it complicates the management of RA. A potential exacerbation of ILD has been reported with all the basic treatments of RA even if the doubt persists on a potential inducing toxic lesions of of these drugs. Biologicals have considerably Improved prognosis and quality of life for patients but many studies also mention a induction or exacerbation of a ILD especially for TNF antagonists. An initial evaluation of pulmonary involvement is necessary allowing support based on the benefit / risk ratio of the different drugs. Regular and systematic monitoring is required for to detect a potential aggravation and to take stock between induced exacerbation and progression of the disease in its natural course.

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