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## Methotrexate in interstitial lung disease associated with rheumatoid arthritis☆

### *Metotrexato en la neumopatía intersticial asociada a la artritis reumatoide*

*Dear Editor:*

After reading with interest the article by Carrasco Cubero et al.,[1] we would like to highlight the remarkable work undertaken, which is necessary to improve the understanding of a clinically relevant aspect such as the relationship between different drugs, including methotrexate (MTX) and rheumatoid arthritis-related interstitial lung disease (RA-ILD). Although we agree with most of the results of the review, and the authors' opinion about them, we feel it necessary to comment on a recommendation in the conclusions: "It is not necessary to discontinue MTX in patients with RA-ILD, as there is evidence that does not increase the incidence or exacerbation of ILD and it improves survival. . ." .

The involvement of MTX in pulmonary comorbidity in some RA patients is an unresolved clinical issue. In a sub-analysis of the CIRT trial[2] (a controlled clinical trial analysing the effect of weekly low-dose MTX on the incidence of major cardiovascular events in a population at high baseline risk), patients treated with low-dose MTX (15−20 mg/week) had a higher risk of developing pulmonary adverse events than those in the placebo group (HR: 1.42; 95% CI: 1.14–1.77), a risk that tripled for serious pulmonary adverse events (HR: 2.99; 95% CI: 1.34–6.65). Although in the Spanish study,[3] MTX combined with abatacept did not cause lung deterioration, in another recent study in Japan[4] examining 131 patients with RA-ILD treated with abatacept, the authors found that the main risk factor for lung disease deterioration was the use of MTX combined with abatacept.

Acute MTX-associated pneumonitis (MTX-Pneum) was described more than 30 years ago, and manifests as an acute or subacute condition with dyspnoea, cough, and pulmonary infiltrates; it is most common in the first months of treatment, and is caused by a dose-independent hypersensitivity mechanism. RA-associated interstitial lung disease (RA-ILD), on the other hand, usually presents insidiously and has different clinical and course characteristics. It is important to remember that RA-ILD is a serious disease that, in many cases, drastically shortens the life expectancy of these patients, who are very complex to manage. Its presence makes it unlikely that the disease as a whole can be controlled with MTX in monotherapy.[5] In our opinion, most patients will require biological treatment, which can control the joint inflammatory process and the progression of the lung disease. Furthermore, clinical trials are currently underway on RA-ILD based on anti-fibrotic drugs that have already proven effective in idiopathic pulmonary fibrosis, with promising results.

Although the involvement of MTX in the onset or progression of RA-ILD has been defined, its prescription or maintenance in patients with RA-ILD is a clinical decision that should be carefully studied. There is scientific evidence that pre-existing RA-ILD is a risk factor for MTX-Pneum.[6,7] However, in patients with known lung disease presenting with acute lung disease, it can be very difficult to differentiate an exacerbation or rapid progression of the underlying chronic process of MTX-Pneum,[8] without invasive tests, such as BAL or cryobiopsy, if the situation allows, which may delay diagnosis and appropriate therapeutic decisions. Moreover, patients with severe forms of RA-ILD, especially those classified under the most frequent subtype, that corresponding to usual interstitial pneumonia, those with progressive fibrosing phenotype, or with associated lower airway pathology, will have limited pulmonary reserve, which would increase mortality if they were to suffer intercurrent MTX-Pneum.

To conclude, we consider that, in patients with RA-ILD, especially if after the corresponding multidisciplinary study, they are classified among the phenotypes with the worst prognosis, MTX should not be prescribed and, if they continue treatment with this drug, our advice is to discontinue it and opt for other therapeutic alternatives, at least until there is sufficient scientific evidence that would entail a change in therapeutic attitude.

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## Neurobehcet's. Comment: "Neuro-Behçet Disease in the Central University Hospital of Asturias"

### *Neurobehcet's. Comentario: "La enfermedad de Neuro-Behçet en el Hospital Universitario Central de Asturias"*

*Dear Editor,*

We read with great interest the manuscript by Charca-Benavente et al., about a frequency and profile of patients with neuro-Behçet's disease at the Central University Hospital of Asturias over a period of 37 years.[1] We have the following comments.

Neurological manifestations, found in 10–30% of the patients with Behcet disease, are recognized in the medical literature as Neurobehçet (NB), were described for the first time in 1941 by Knapp, and in 1954 Cavara & DÉrmo coined the term NB, and include migraine-like headache, aseptic meningoencephalitis, encephalopathy, dementia, seizures, cranial nerve and bulbar palsy, movement disorders, cerebellar ataxia, myelopathy, neurosensorial hearing loss, stroke, psychiatric disturbances, and a multiple sclerosis-like picture.[2] They usually manifest within 5 years of onset. Neurological complications progress to severe disability, with a high mortality rate.[3] Although this broad spectrum of manifestations is widely recognized, myositis is rare.

However, in the study by Charca-Benavente et al., despite a considerable period of analysis, it strikes us that there were no cases of muscle involvement, so we would like to know to what the authors attribute this data.

The authors should have addressed the neuromuscular manifestations of NB.BD must be considered as a differential diagnosis of localized or generalized inflammatory muscle disorders especially when findings of multiple tissue and organ lesions or any symptom of the characteristic triad are present. Given the multisystemic nature of the syndrome, it's not surprising the report of "unusual" manifestations that will further expand the wide spectrum of NB.[2]

We are grateful to the authors for the excellent article addressing a relevant topic within BD, allowing discussion to contribute with knowledge.

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