patients included an exploration of the biopsy site, identifying that it recovered normal characteristics; this may be the result of NTAP application, as it releases free radicals that stimulate angiogenesis and fibroblasts, resulting in an organised tissue repair process.[6,7,10]

In conclusion, with the cases presented, NTAP proved a useful and safe alternative for patients, as tissue regeneration was observed within 72 h following the biopsy, thus avoiding postoperative complications.

References

1. Caraba A, Babalic FC, Iurciuc S, Iurciuc M. The utility of major salivary gland ultrasonographic parameters in the Diagnosis of Sjögren Syndrome. Dis Markers. 2019;2019:1716848, http://dx.doi.org/10.1155/2019/1716848.
2. Chiu Y-H, Lee T, Chao E, Chen I-F, F-Ch Liu, et al. Application of classification criteria of Sjogren syndrome in patients with sicca symptoms: real-world experience at a medical center. J Formosan Med Assoc. 2019;119:480–7, http://dx.doi.org/10.1016/j.jfma.2019.06.012.
3. Lacombre V, Lacout C, Lozac'h P, Ghali A, Gury A, et al. Unstimulated whole saliva flow for diagnosis of primary Sjögren's syndrome: time to revisit the threshold? Arthritis Res Ther. 2020;22:38, http://dx.doi.org/10.1186/s13075-020-2132-3.
4. Trevisani VFM, Posoto SG, Fernandes M, Lopes M, Fialho S. Recommendationes from the Brazilian society of rheumatology for the diagnosis of Sjögren's syndrome (Part I): glandular manifestations (systematic review). Adv Rheumatol. 2019;59:58, http://dx.doi.org/10.1186/s42358-019-0102-8.
5. Vinke J, Kaper HJ, Vissink A, Sharma PK. Dry mouth: saliva substitutes which adsorb and modify existing salivary condition films improve oral lubrication. Clin Oral Invest. 2020, http://dx.doi.org/10.1007/s00784-020-03272-x.
6. López-Callejas R, Peña-Eguiluz R, Valencia-Alvarado R, Mercado-Cabrera A, Rodríguez-Méndez BG, et al. Alternative method for healing the diabetic foot by means of a plasma needle. Clin Plasma Med. 2018;9:19–23, http://dx.doi.org/10.1016/j.cpme.2018.01.001.
7. Betancourt-Ángeles M, Peña-Eguiluz R, López-Callejas R, Domínguez-Cadena NA, Mercado-Cabrera A, et al. Treatment in the healing of burns with a cold plasma source. Int J Burn Trauma. 2017;7:142–6. PMID: 29348977; PMCID: PMC5768930.
8. Derikvand N, Chinipardaz Z, Ghasemi S, Chiniforush N. The versatility of 980 nm Diode laser in dentistry: a case series. J Lasers Med Sci. 2016;7:205–8, http://dx.doi.org/10.15171/jlms.2016.36.
9. Delli K, Dagal EF, Bootmas H, Vissink A, Spijkervet FK. Patient-reported change of sensibility and pain after parotid and labial gland biopsy applied for primary Sjögren' syndrome diagnostics: one-year follow-up study. Clin Exp Rheumatol. 2018;112 36 Suppl:S173–6. PMID: 30156543.
10. Brun P, Pathak S, Castagliuolo I, Palú G, Brun P, Zuin M, et al. Helium generated cold plasma finely regulates activation of human fibroblast-like primary cells. PLoS One. 2014;9, http://dx.doi.org/10.1371/journal.pone.0104397.

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Answer to the Letter to the Editor: Methotrexate in interstitial lung disease associated with rheumatoid arthritis☆

Respuesta a la carta al editor: Metotrexato en la neumopatía intersticial asociada a la artritis reumatoide

Dear Editor,

We appreciate the interest shown by Arboleya-Rodríguez[1] in our original: "Systematic Review of the Impact of Drugs on Diffuse Interstitial Lung Disease Associated with Rheumatoid Arthritis (RA-DILD)"[2] and his critical comment on one of the conclusions given in our article: "It is not necessary to discontinue methotrexate (MTX) in patients with RA-DILD, as there is evidence that it does not increase the incidence or exacerbations of DILD and improves survival".

We did not include acute MTX pneumonitis (idiosyncratic hypersensitivity reaction) in our PICO question[2]. We believe that it cannot be claimed that RA-associated DILD predisposes to the development of acute MTX pneumonitis based on a single retrospective study conducted in the 1980s[3]. We emphasise the value of systematic reviews (SR) rather than individual studies to search for evidence that is useful for clinical practice. The evidence found in our SR[2] indicates that MTX does not increase either the incidence or exacerbations of RA-DILD.

The aim of treatment should be to control RA without worsening the course of the DILD. When MTX is part of the treatment, the decision to continue or discontinue it should be tailored to the individual patient. However, there is growing evidence that rather than being discontinued, MTX has an important role to play in the treatment of patients with RA-DILD[2,4–6].

Of the other two articles mentioned by Arboleya to advise discontinuing MTX in patients with RA and DILD, one is a retrospective study[7], without a control group, of a single-centre case series that was included in our SR[2], and our analysis can be found there. The other is the CIRT trial[8] (published after our SR[2]), conducted in patients with cardiovascular disease and metabolic syndrome or diabetes to investigate the side effects of MTX versus placebo. Patients with systemic rheumatic diseases and/or interstitial lung disorders were excluded from this clinical trial. They found episodes consistent with acute pneumonitis in six of the 3291 patients allocated to MTX and one of the 2080 allocated to placebo (HR 6.94 [95% CI .85–56.0]), but in no case was this considered likely or definitive on adjudication. Therefore, no conclusions can be drawn from this study on the performance of MTX in RA-DILD.

In conclusion, we believe that it is very important to control the inflammatory activity of RA without worsening the progression of DILD. When these patients need biological therapy, abatacept or rituximab is preferable to anti-TNF (with more potential risk) or targeted synthetic disease-modifying antirheumatic drugs (DMARDs), given the lack of evidence. Treatment should always be individualised. In this context, it does not seem necessary to discontinue MTX in patients with AR-DILD, as there is evidence that it increases neither the incidence nor exacerbations of RA-DILD and it improves survival.

References

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1. Arboleya-Rodríguez L, Arias-Gillén M. Metotrexato en la neumopatía intersticial asociada a la artritis reumatoide. Reumatol Clin. 2020, http://dx.doi.org/10.1016/j.reuma.2020.10.011.
2. Carrasco Cubero C, Chamizo Carmona E, Vela Casasempere P. Revisión sistemática sobre el impacto de los fármacos en la enfermedad pulmonar intersticial difusa asociada a Artritis Reumatoide. Reumatol Clin. 2020, http://dx.doi.org/10.1016/j.reuma.2020.04.015.
3. Golden MR, Katz RS, Balk RA, Golden HE. The relationship of preexisting lung disease to the development of methotrexate pneumonitis in patients with rheumatoid arthritis. J Rheumatol. 1995;22:1043–7.
4. Rojas-Serrano J, Herrera-Bringas D, Pérez-Román DI, Pérez-Dorame R, Mateos-Toledo H, Mejía M. Rheumatoid arthritis-related interstitial lung disease (RA-ILD): methotrexate and the severity of lung disease are associated to prognosis. Clin Rheumatol. 2017;36:1493–500.
5. Fernández-Díaz C, Castañeda S, Melero R, Loricera R, Ortiz-Sanjuán F, Jun-Mas A, et al. Interstitial lung disease: national multicenter study of 263 patients. Ann Rheum Dis. 2020;79 Suppl. 1:968.
6. Nokhatha SA, Harrington R, Conway R. Is methotrexate contra-indicated in lung involvement of rheumatoid arthritis? Joint Bone Spine. 2020, http://dx.doi.org/10.1016/j.jbspin.2020.06.007.
7. Mochizuki T, Ikari K, Yano K, Sato M, Okazaki K. Long-term deterioration of interstitial lung disease in patients with rheumatoid arthritis treated with abatacept. Mod Rheumatol. 2019;29:413–7.
8. Solomon D, Glynn RJ, Karlson E, Lu F, Corrigan C, Colls J, et al. Adverse effects of low-dose methotrexate: a randomized trial. Ann Intern Med. 2020;172:369–80.

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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.

References

1. Carrasco Cubero C, Chamizo Carmona E, Vela Casasempere P. Revisión sistemática sobre el impacto de los fármacos en la enfermedad pulmonar intersticial difusa asociada a Artritis Reumatoide. Reumatol Clin. 2021;17:504–13, http://dx.doi.org/10.1016/j.reuma.2020.04.015.
2. Solomon D, Glynn RJ, Karlson E, Lu F, Corrigan C, Colls J, et al. Adverse effects of low-dose methotrexate: a randomized trial. Ann Intern Med. 2020;172:369–80.

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