



Letters to the Editor

Severe Secondary Bone Marrow Aplasia Due to Methotrexate in a Patient With Late Onset Rheumatoid Arthritis[☆]



Aplasia medular grave secundaria a intoxicación por metotrexato en un paciente con artritis reumatoide de inicio senil

To the editor:

Methotrexate (MTX) is the disease modifying antirheumatic drug (DMARD) most commonly used in the treatment of rheumatoid arthritis (RA). It is recommended as first-line DMARD by the European League against Rheumatism (EULAR) and the American College of Rheumatology (ACR), alone or in combination with other DMARDs and biological agents. The most common side effects associated with the use of low-dose MTX are gastrointestinal manifestations and elevated liver enzymes, followed by neurological symptoms (headache, fatigue, and dizziness) and cytopenias, mainly leucopenia.¹

In patients with RA treated with MTX, the prevalence of hematologic toxicity, including leukopenia, thrombocytopenia, pancytopenia and megaloblastic anemia, is estimated at 3%.^{2,3} The degree of pancytopenia, an adverse effect which may be severe and unpredictable, even at low doses of MTX, may be underestimated. The mortality of severe MTX-induced pancytopenia is unknown. In a series of 25 cases reported by the University Hospital of Norfolk and Norwich, it was estimated at 28%.³

We report the case of a male patient aged 82, independent in his daily activities, ex-smoker, recently diagnosed as diabetic and diagnosed with RA 6 years prior. He was treated with MTX at the beginning RA, with oral doses of 7.5 mg/week, associated with folic acid weekly. After 3 years of treatment, with no side effects and the disease being inactive, he suspended MTX and continued monitoring by his primary care physician. The patient came to the emergency room for malaise, bleeding and painful oral ulcers for 2 months and with melanic evacuations in the past week; he did not refer fever at home, and had poor temperature regulation and respiratory symptoms. Upon interrogation he said that since 2 and half months prior he had an exacerbation of joint manifestations; he was again taking MTX orally at doses of 7.5 mg but administered daily until the time of hospitalization, without folic acid and no other medication that could increase the toxicity of MTX. Physical examination included: temperature 38.4 °C, blood pressure 85/56 mmHg, heart rate 150 bpm, respiratory rate 32 rpm, baseline oxygen saturation 95%. Mucositis bleeding, petechiae

and ecchymosis of the chest and limbs were observed. Cardiac sounds were arrhythmic and he had crackles in the right lung base upon auscultation. In the laboratory analysis we highlighted the following: hemoglobin 7.8 g/dl, MCV 103.1 fL, WBC 500/mm³, neutrophils 160/mm³, platelets 3000/mm³, prothrombin 56%, creatinine 1.1 mg/dl, aspartate aminotransferase 97 U/l, alanine aminotransferase 128 U/l, total bilirubin 2.80 mg/dl (direct 2.10 mg/dl), CRP >90 mg/l, folate 15.8 ng/ml and vitamin B12 514.4 pg/ml. Chest X-ray showed interstitial alveolar infiltrates, parahilar on the right lung. Chest CT revealed diffuse areas of ground-glass opacities, subpleural increased crosslinking in the right upper lobe; laminar atelectasis in the middle lobe; left pleural effusion. Diagnostic thoracentesis included exudate and inflammatory fluid cytology with reactive mesothelial cells. Negative microbiological studies were observed for blood cultures, Legionella and pneumococcal urinary antigen, and cultures of pleural fluid, sputum and urine.

The patient required entry into the ICU for clinical pulmonary sepsis and severe pancytopenia. He had been taking a dose of 7.5 mg/day of MTX for more than a month without folic acid supplementation. The problem was interpreted as toxicity secondary to MTX. He was treated with broad-spectrum antibiotics, hydration, granulocyte colony stimulating factor, folic acid and IV methylprednisolone. He received several transfusions of packed red blood cells and platelets, and presented episodes of rapid atrial fibrillation which were controlled with amiodarone and beta blockers. The patient had a good clinical and analytical outcome with resolution of pulmonary infiltrates, improvement of mucositis and rapid recovery of the white series and platelets. The red series has had a slower response to treatment, with persistent normocytic anemia 3 months after discharge.

Pancytopenia is a rare complication of treatment with MTX which can sometimes be fatal. In most cases it is transient and recovers after discontinuation of the drug, but in some patients it causes severe and irreversible pancytopenia, which may result in death.⁴ MTX toxicity can occur in the absence of specific identifiable risk factors, but it has been seen that there are several factors that can affect its development, such as low renal glomerular filtration, advanced age, interaction with other drugs, poor nutritional status with hypoalbuminemia, increased levels of free drug in plasma and hidden chronic liver disease, so this must be taken into account before starting MTX.^{3,4} It is estimated that the incidence and prevalence of MTX pneumonitis is 3.9 and 5.5%, respectively, and in most cases drug withdrawal leads to clinical and radiological improvement over a few weeks.⁵ In our case, we assume that pneumonitis was due to MTX because the patient did not refer previous respiratory problems, an X-ray a year earlier showed no interstitial pattern and after discontinuation of the drug there was radiographic improvement within months.

With respect to the prescription dose, there have been numerous warnings to the Spanish Agency for Medicines and Health Products of serious reactions to MTX due to a confusion in the

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administered dose, taking it daily instead of weekly,⁶ which is what happened in our case.

Use extreme caution when prescribing MTX, especially in elderly patients, and careful prescription, not only verbally but also in writing, of the dose to be administered weekly as well as insisting on these to both the patients and the relatives and primary care professionals, are needed in order to avoid serious complications.

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Triple therapy with non-biologic DMARDs for rheumatoid arthritis or biologic therapy. Is it the same?



Triple terapia con FARME no biológico o tratamiento biológico para artritis reumatoide. ¿Son lo mismo?

The goals for rheumatoid arthritis (RA)—remission or low disease activity—are achieved through combination therapy with disease-modifying antirheumatic drugs (DMARDs) or biologic therapy. DMARDs combination therapy achieve the goals in higher percentage than DMARD monotherapy^{1,2}. Recently O'Dell et al. compared triple therapy with three non-biologic DMARDs, and biologic therapy with etanercept-methotrexate in RA³. This comparison is important for developing countries because the poor availability through social security⁴.

O'Dell and colleagues did not find significant differences in DAS28 (using erythrocyte sedimentation ratio, ESR or C reactive protein, CRP). Even DAS28 is considered the “gold standard” for evaluating disease activity, other clinical measures such as ultrasound or MRI might improve sensitivity for the targets in RA patients⁵⁻⁸. The study reported that patients receiving biologic therapy achieved American College of Rheumatology ACR50 and ACR70 almost 10% higher than triple therapy. Previous studies informed improved productivity of daily work and slow or not radiographic progression in patients under biologics therapy, although the significance related with the structural differences is not clinically defined^{1,9,10}. It is clear that there are benefits for patients receiving biologic therapy.

The clinical benefits of triple therapy previously mentioned are relevant in most RA patients when compared to efficacy of DMARD combination. This is especially an attractive treatment because of the lower cost of triple therapy compared to biologics, particularly in developing countries. Although we do not have official data related with social security in México, approximately 20% of RA patients covered by ISSSTE (11% of total Mexican population), and less than 5% of IMSS (59% of total Mexican population) are receiving a biological therapy; Mexican population with no social security is a rare event to prescribe biologic therapy. However, although triple therapy can be more accessible than biologics, the latter treatment becomes necessary for at least in 20-30% of RA patients particularly when individual treatment is refractory to methotrexate. Nonetheless, treatments with higher doses of methotrexate^{11,12}, in combination with prednisone¹³ or with another combination

of DMARD, reduces the percentage of patients requiring biologics therapy^{1,14,15}. We suggest that initial triple DMARDs therapy for RA as the first therapy for monotherapy non-responsive patients and biologics must be reserved for refractory triple DMARDs therapy.

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