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Case report

Severe leukopenia in a rheumatoid arthritis patient treated with a methotrexate/leflunomide combination☆

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ABSTRACT

A rheumatoid arthritis patient was treated for two years with methotrexate and leflunomide combination therapy. The evolution was uneventful until she had clopidogrel, simvastatin, isosorbide, aspirin and omeprazole added to medication due to acute myocardial infarction. Four weeks after this, she was hospitalized with severe leukopenia.

Leucopenia grave em paciente com artrite reumatoide tratada com combinação de metotrexato e leflunomida

Palavras-chave:
Artrite reumatoide
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RESUMO

Apresentamos o caso de uma paciente com artrite reumatoide tratada por dois anos com associação de metotrexato e leflunomida. A paciente foi internada com leucopenia grave quatro semanas após acrescentar ao esquema medicamentoso as drogas clopidogrel, isosorbida, sinvastatina, AAS e omeprazol.

Introduction

Methotrexate (MTX) is considered as a basic drug for most therapeutic regimes for rheumatoid arthritis worldwide.[1] However, its use as monotherapy, or associated only with low dose corticosteroids, is often insufficient for remission induction or to achieve acceptable levels of disease activity. Therefore, various combination therapies have been tested in order to increase the efficiency of MTX. Among these, the association with leflunomide (LEF) proved the most effective, with synergistic effects demonstrated in several studies.[2] Nevertheless, the possibility of cumulative toxicity of the two drugs is always a concern, whenever this drug combination is prescribed.

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Case report

In January 2011, a 68-year-old woman was hospitalized in the Department of Internal Clinic of HSPE with dyspnea on exertion, fatigue, lack of appetite, diarrhea, cough, fever and chills. The patient showed a regular general state and her admission was justified by the results of a CBC in the emergency department: Hemoglobin (HB): 10 mg/dL (HTC: 31.2, MCV: 92.3, MCHC: 32.0, RDW: 16.5); leukocytes: 980/mm^3 (neutrophils, 500; lymphocytes, 300; eosinophils, 80; and monocytes, 100); platelets: 182.000/mm^3.

Her pathological history revealed rheumatoid arthritis for six years, mainly with proximal interphalangeal joints, metacarpophalangeal joints and wrists involved. In January 2008 she started treatment with methotrexate 15 mg weekly with folic acid supplementation at a dose of 5 mg two days after taking MTX. In January 2010 the patient had persistent synovitis in the mentioned joints, requiring 10 mg/day of prednisone to control the painful symptoms. On this occasion, the addition of leflunomide 20 mg/day started, with reduction of methotrexate to 10 mg weekly and maintenance of the replacement schedule of folic acid.

With this therapeutic regime, the patient obtained good clinical response, remission of synovitis and progressive improvement of joint pain. She did not relate significant side effects during the year of 2010.

In October 2010, her medical record indicated outpatient care; the patient was virtually symptom free and without synovitis. In this occasion, a CBC yielded the following results: HB 10.8 mg/dL; leukocytes: 4850/mm^3 (neutrophils, 3500; eosinophils, 200; lymphocytes, 700; and monocytes, 450); platelets: 290.000/mm^3. Liver enzymes values were within the normal range.

In December 2010, the patient was admitted to the Coronary Care Unit of HSPE with typical precordial pain, and a diagnosis of acute myocardial infarction (AMI) was confirmed. Due to this event, she began clopidogrel, aspirin, isosorbide, simvastatin and omeprazole continuously, in addition to medication for rheumatoid arthritis, and maintained this therapeutic regime until new hospitalization, reported above, four weeks after AMI.

Progression

In the ward, the patient received antibiotic coverage according to the protocol for patients with febrile leukopenia. Considering the possibility of myelotoxicity, MTX and LEF were suspended, the dose of prednisone was increased to 20 mg/day, and folinic acid was initiated at a dose of 15 mg/day.

On this therapeutic scheme the patient showed rapid improvement. A CBC obtained three days after the beginning of the replacement with folinic acid showed the following results: HB: 8.7 mg/dL (HTC 28, MCV 81); leukocytes: 3.130 (neutrophils, 220; eosinophils, 200; lymphocytes, 430; monocytes, 300); platelets: 202,000; VHS: 80.

Given a favorable and constant evolution, the patient was discharged after 10 days without antibiotics and only with her heart medication plus folinic acid 15 mg/d and prednisone 5 mg/d.

In the last follow-up (May, 2011), the patient was asymptomatic, with the following laboratory data: ALT: 12 U/L, AST 13 U/L; hemoglobin: 12.6 mg/dL; MCV 88.3 fL; WBC: 8700/mm^3 (neutrophils, 6700; eosinophils, 300; lymphocytes, 1200; monocytes, 500); platelets: 398,000.

Discussion

Although not all mechanisms by which MTX exerts its anti-inflammatory activity in rheumatoid arthritis are known, its primary pharmacological action is to block the enzyme folate reductase by interfering with the synthesis of nucleotides in the purine pathway.

Leflunomide (LEF) inhibits the synthesis of nucleotides in the pirimidine pathway, with a possible synergistic action with MTX in reducing the activity of immunocompetent cells.

The concomitant use of MTX and LEF provides additional benefits, compared to each of these agents as monotherapy.[2]

However, the combination of MTX with LEF is considered risky, for there is the possibility of an additive toxicity of both drugs on liver, lung and bone marrow. For that reason, their association is formally contraindicated in USA. In Brazil, Australia and New Zealand, many rheumatologic centers accept this association, which is considered safe in relation to the possibility of liver toxicity.[3] Thus, this combination was seen as another step in RA therapeutic pyramid.[4]

In the present case, a LEF-MTX combination showed a good result in the control of rheumatoid disease, providing a smooth evolution until a new clinical event (AMI) required the addition of drugs of common usage for the clinical situation related, but this new circumstance probably interacted in the genesis of myelotoxicity, resulting in leukopenia. Among the drugs with positive interaction with MTX, we found ASA[5] and omeprazole in the patient's prescription. These drugs can increase the persistence and availability of MTX in plasma.[6,7]

Conflicts of interest

The authors declare no conflicts of interest.

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