Case Report

Severe Bone Marrow Suppression Accompanying Pulmonary Infection and Hemorrhage of the Digestive Tract Associated with Leflunomide and Low-dose Methotrexate Combination Therapy

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Abstract

A 60-year-old male patient developed hyperpyrexia, cough, expectoration with blood-stained sputum, mouth ulcers, and suppurative tonsillitis after receiving 35 days of combination treatment with leflunomide (LEF) and low-dose methotrexate (MTX) for active rheumatoid arthritis. On admission, routine blood tests showed severe thrombocytopenia, agranulocytosis, and decreased hemoglobin concentration compared with the relatively normal results of 1 month previously during the first hospitalization. Chest radiography revealed inflammation in both lungs, and a fecal occult blood test was positive. Given this presentation, severe bone marrow suppression accompanying pulmonary infection and hemorrhage of the digestive tract associated with LEF and MTX combination therapy was diagnosed. After 28 days of symptomatic treatment, the patient's complications subsided gradually. This case highlighted that bone marrow suppression associated with MTX and LEF combination therapy could be very serious, even at a normal dose or especially at the beginning of treatment. MTX and LEF combination therapy should be used with caution or be limited in those with a history of pulmonary disease, hemorrhage of the digestive tract, or other relevant diseases.

Keywords: Adverse drug reaction, leflunomide, methotrexate, pulmonary infection, severe bone marrow suppression

Introduction

Methotrexate (MTX) and leflunomide (LEF) are both effective first-line disease-modifying antirheumatic drugs (DMARDs) used for the treatment of active rheumatoid arthritis (RA). The potentially complementary mechanisms of action of these two effective DMARDs provide a rationale for their use in combination therapy for patients whose condition no longer responds to MTX alone.[1]

In general, low-dose MTX and LEF combination therapy in RA patients is safe and well tolerated, with adverse events comparable with those of monotherapy and other nonbiological DMARDs treatments.[2] The most commonly reported adverse events related to MTX and LEF, namely, diarrhea, nausea, alopecia, rash, headache, and elevated plasma liver enzyme are generally mild to moderate and resolve without complications.[3] However, serious adverse drug reactions (SADRs) such as liver disease,[4] pancytopenia,[5] and severe leukopenia, in addition to opportunistic infections and toxic epidermal necrolysis,[6,7] can result in discontinuation of therapy or hospitalization. Here, we described the first case, to our knowledge, of a 60-year-old male patient with RA who developed severe bone marrow suppression accompanying pulmonary infection and hemorrhage of the digestive tract associated with low-dose MTX and LEF combination therapy.

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Case Report

A 60-year-old man was admitted to the Third Affiliated Hospital of Sun Yat-sen University, China, for the first time on September 16, 2013 because of 4 years of swelling and pain in bilateral metacarpophalangeal, knee, proximal and distal interphalangeal, ankle, and wrist joints, accompanied by 3 days of fever and chills, coughing, and expectoration. On the 2nd day after admission, important laboratory investigations such as blood counts, serum chemistries, and blood coagulation function were carried out and are shown in Table 1. The patient had no history of hepatitis and serological tests for hepatitis A virus, hepatitis B virus, hepatitis C virus, hepatitis E virus, and human immunodeficiency virus were clear. His medical history revealed that he had experienced hemorrhage of the upper digestive tract and pulmonary infection and consequently received antigout, anti-infectious, and acid suppressive treatment as well as protection of gastric mucosa 42 days before admission. However, he had not received any antirheumatoid treatment before presenting for the first time. He was diagnosed with active RA on evaluation of laboratory tests, clinical symptoms, and radiology. After admission, the patient received 1 week of ceftizoxime (1.5 g, twice daily, drip) for anti-infection, 2 weeks of ^{99}Tc-methylendiphosphonate (16.5 mg, once daily, injection) for anti-inflammation, and 7 days of oral antirheumatoid therapy including LEF (20 mg/day), MTX (10 mg/week), celecoxib (0.2 g/day), and methylprednisolone (8 mg/day). His condition improved and he was discharged with a white blood cell (WBC) count of 5.43 × 10^9/L, hemoglobin concentration of 78 g/L, and platelet count of 362 × 10^9/L. On discharge, oral combination therapy for RA comprising LEF, MTX, celecoxib, and methylprednisolone was continued; pantoprazole (40 mg/day), teprenone (50 mg, 3 times daily), and caltrate D (600 mg/day) were also prescribed orally as an adjuvant therapy intended to inhibit gastric acid secretion, provide gastric mucosal protection, and prevent osteoporosis associated with methylprednisolone.

Table 1: The initial laboratory investigations during the first hospitalization

Measurement	Value	Reference range
Hematological panel		
WBCs (×10^9/L)	7.73	3.50-9.50
Neutrophilic granulocyte (%)	74.9	50.00-70.00
Red blood cells (×10^{12}/L)	2.61	4.30-5.80
Hemoglobin concentration (g/L)	70	130-175
Platelets (×10^9/L)	311	100-350
Serum chemistry results		
Aspartate aminotransferase (U/L)	16	15-40
Alanine aminotransferase (U/L)	11	3-35
Erythrocyte sedimentation rate (mm/h)	148.0	0-20
C-reactive protein (mg/L)	59.70	0.00-6.00
Albumin (g/L)	28.9	36-51
Globulin (g/L)	23.2	25-35
Total complement (U/mL)	56	23-46
Rheumatoid factor (IU/ mL)	10.1	0.0-20.0
Immunoglobulin G (g/L)	11.86	8.00-16.00
Blood urea nitrogen (mmol/L)	9.2	2.4-8.2
Creatinine (μmol/L)	146.4	31.8-116.0
Uric acid (μmol/L)	486.4	90-420
Tubercle bacillus antibody test	Negative	Negative
Blood coagulation function		
Prothrombin time (s)	15.8	11.0-14.5
Activated partial thromboplastin time (s)	39.1	28.0-41.0
Plasma fibrinogen level (g/L)	5.54	2.00-4.00
Thrombin time (s)	15.9	14.0-21.0

WBCs=White blood cells

On the 1st day after admission, laboratory examinations revealed an obvious decrease in platelet count (6 × 10^9/L), WBC count (0.53 × 10^9/L with neutrophil count of 0.03 × 10^9/L), and hemoglobin concentration (51 g/L) compared with results from the first hospitalization. On the 2nd day, abnormal serum chemistry results included aspartate transaminase 66 U/L, alanine aminotransferase 299 U/L, C-reactive protein 197.8 mg/L, erythrocyte sedimentation rate 140 mm/h, blood urea nitrogen 11.05 mmol/L, uric acid 466.4 μmol/L, and serum creatinine 182.1 μmol/L. The fecal occult blood test was positive. Chest radiography revealed inflammation in both lungs. Given this presentation, severe bone marrow suppression accompanying pulmonary infection and hemorrhage of the digestive tract associated with MTX and LEF combination therapy was diagnosed. Combination therapy of MTX and LEF was stopped, and celecoxib was also suspended because of possible liver toxicity. Imipenem and cilastatin (1 g 3 times daily, drip) and vancomycin (0.5 g 3 times daily, drip) were prescribed to control infection in the lungs. Reduced glutathione was also administered by injection (1.2 g/day, drip) to provide liver protection. The dosage of pantoprazole was stepped up to 40 mg every 12 h for 3 days, and iodine glycerin was applied locally to relieve pain resulting from mouth ulcers. Meanwhile, other intensive supportive therapy was also implemented, including parenteral nutrition, transfusion of red cells and platelets, and use of recombinant human granulocyte colony-stimulating factor (300 μg/day injection) to increase the leukocyte count. The patient's complications subsided gradually after 28 days of symptomatic treatment. He was discharged with a normal blood count, normal body temperature, negative fecal occult blood test, coalesced mouth ulcers, normal liver function, and improved chest radiograph as well as remission of other symptoms. However, LEF/MTX/celecoxib combination therapy was replaced by the Chinese patent medicine leigongtengduodai (20 mg, 3 times daily, oral) and hydroxychloroquine sulfate (200 mg, twice

daily, oral) in combination with oral methylprednisolone (8 mg/day). Routine blood tests were normal at the 2-week and 1-month follow-up visits.

Discussion

A score of 7 on the Naranjo Adverse Drug Reaction Probability Scale[8] for this case of severe bone marrow suppression after low-dose MTX and LEF combination therapy suggests a probable adverse drug reaction. First, there was temporal causation because the SADR occurred after MTX and LEF combination therapy was administered. Second, bone marrow depression has been recorded in regimens of both MTX and LEF as reported in literature.[5,6] Third, discontinuation of MTX and LEF combination therapy and the use of symptomatic treatment resulted in marked improvement of our patient's condition, suggesting that a drug-related adverse reaction had occurred. Fourth, although other concomitant agents, such as celecoxib, can cause gastrointestinal damage and increase bleeding risk,[9] hematologic toxicity associated with celecoxib has not been reported thus far. However, methylprednisolone can stimulate the hematopoietic function of bone marrow, increasing the number of circulating neutrophils and platelets as well as inducing erythropoiesis; moreover, as the actions of several other agents included in adjuvant therapy are mild without side effects of this type, the contribution of other concomitant agents can be excluded. Finally, because routine blood tests were without peculiarity before the MTX and LEF combination therapy and during the 1st week of treatment, the possibility of hematologic disease was scarce. Nevertheless, a history of hemorrhage of the upper digestive tract and pulmonary infection has an association with the occurrence of complications and celecoxib as well as methylprednisolone can possibly aggravate hemorrhage of the digestive tract.

The mechanism by which a SADR occurred in our patient may be as follows. First, a possible synergistic action of MTX and LEF for their depressive effects on bone marrow should be considered as both can interfere with the synthesis of nucleotides and/or further reduce the activity of immunocompetent cells.[5] Second, the patient's hypoalbuminemia can raise the free concentration of the bioactive metabolite of LEF and enhance its toxicity probably. Third, genetic factors may also contribute to the significantly increased risk of predisposition to pulmonary infection and tolerability.[10] Fourth, the patient's relatively poor kidney function and decreased creatinine clearance can cause the accumulation of MTX and strengthen its hematological toxicity possibly. Finally, it is possible that MTX and LEF combination therapy without folic acid supplementation can aggravate the hematologic toxicity of MTX.

Conclusion

Clinicians should be alert to severe bone marrow suppression and the subsequent or accompanying serious complications, such as opportunistic infections and hemorrhage of the digestive tract, when prescribing MTX and LEF combination therapy. It is strongly recommended that regular monitoring of blood counts should be implemented to appropriately identify the degree of bone marrow suppression, especially during the first 3 months of treatment. Moreover, supplementary folic acid should also be prescribed as adjuvant therapy to decrease the hematologic toxicity of MTX and LEF in combination. When blood counts decline rapidly, therapy with MTX and LEF should be stopped immediately. For patients with a history of pulmonary disease or hemorrhage of the digestive tract, combined MTX and LEF may be inappropriate.

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Conflicts of interest

There are no conflicts of interest.

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