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CASE SERIES

Pancytopenia Due to Possible Drug–Drug Interactions Between Low-Dose Methotrexate and Proton Pump Inhibitors

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Abstract: Methotrexate (MTX) has been widely used with a wide range of doses in the treatment of certain neoplastic diseases, severe psoriasis, and rheumatoid arthritis. At higher dose, monitoring of serum MTX elimination is performed because delayed elimination can result in serious and potentially life-threatening toxicities. A number of medications, including nonsteroidal anti-inflammatory drugs (NSAIDs), salicylates, phenylbutazone, phenytoin, sulfonamides, and some oral antibiotics, are known to interact with MTX therapy through various mechanisms. Accumulating evidence suggests that concomitant use of MTX (primarily at high doses) and proton pump inhibitors (PPIs) such as omeprazole, esomeprazole, and pantoprazole may decrease MTX clearance. The majority of the reported cases occurred with the administration of high-dose MTX in patients receiving doses of 300 mg/m^2 to 12 g/m^2. However, there were also cases of patients taking PPI and experiencing toxicity at doses as low as 10 mg of MTX per week. Although the dosage of MTX is small, the presence of side effect may be delayed and still dangerous. After literature review, it was found that common toxicities associated with low-dose MTX used for inflammatory arthritis include gastrointestinal adverse effects (>10%; ie nausea, stomatitis) and central nervous system toxicity (~20%; ie fatigue, malaise, dizziness, impaired cognition) with weekly administration. Bone marrow suppression (<3%; ie leukopenia, neutropenia, thrombocytopenia) and hepatotoxicity (~15%; ie reversible elevations in transaminases) are less common, and rarely MTX can also cause pulmonary (<1%) and other toxicities. Here, we report two cases who presented with severe pancytopenia 8 and 13 days after taking low-dose MTX and PPI. We highlight that in absence of risk/benefit ratio correctly set, an assessment of appropriateness of PPI prescription before MTX therapy can limit an iatrogenic risk.

Keywords: low-dose methotrexate, proton pump inhibitors, pancytopenia, drug–drug interactions

Cases Presented

The first case was a 50-yr-old Chinese female with rheumatoid arthritis for 12 years without medication. Baseline blood test indicated that hemoglobin 95 g/l, white blood cell count 3.73 × 10^9/l, platelets 190 × 10^9/l, serum creatinine 107 μmol/l, eGFR 52 mL/min/1.73m^2, and albumin 21 g/l. After admission, she was given omeprazole 40 mg per day on April 23 of year 2020, hydroxychloroquine 0.1g twice a day on April 18 and MTX 10mg twice on April 18 and April 25 respectively. After 8 days (April 30) of combination of omeprazole and MTX, she presented severe pancytopenia (Table S1). We stopped MTX immediately and stopped omeprazole on May 9, meanwhile, calcium folinate, GCSF, methylprednisolone and thrombopoietin agonists were taken to rescue the toxicity of methotrexate. Her severe pancytopenia improved on May 11. We monitored the plasma concentration of Methotrexate <0.05 μmol/l on May 10.

The second case was a 68-yr-old Chinese female with rheumatoid arthritis for 20 years. She has taken MTX 10mg weekly and folic acid 10 mg per day more than 20 years. Her hemoglobin was 81 g/l, white blood cell count 3.38 × 10^9/l, platelets 111 × 10^9/l, creatinine 91 μmol/l, eGFR 56 mL/min/1.73m^2, and albumin 22.8 g/l on admission. She was given

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omeprazole 20mg per day on April 10 of year 2020, hydroxychloroquine 0.1g twice a day on April 18 and MTX 10mg twice on April 14 and April 21 respectively. After 13 days (April 26) of combination of omeprazole and MTX, she presented severe pancytopenia (Table S2). We stopped MTX immediately and stopped omeprazole on April 22, meanwhile, calcium folinate, GCSF, methylprednisolone and thrombopoietin agonists was taken to rescue the toxicity of methotrexate. Her severe pancytopenia improved on May 5. We did not monitored her plasma concentration of methotrexate.

Results

Both cases presented with severe pancytopenia in the hospital without bleeding, infection, and hepatosplenomegaly (Figures 1 and 2). They had normal serum levels of folic acid and vitamin B12. Both cases showed normal in bone marrow smear. Neither of them had joint pain or swelling or increased level of C-reactive protein, ruling out disease

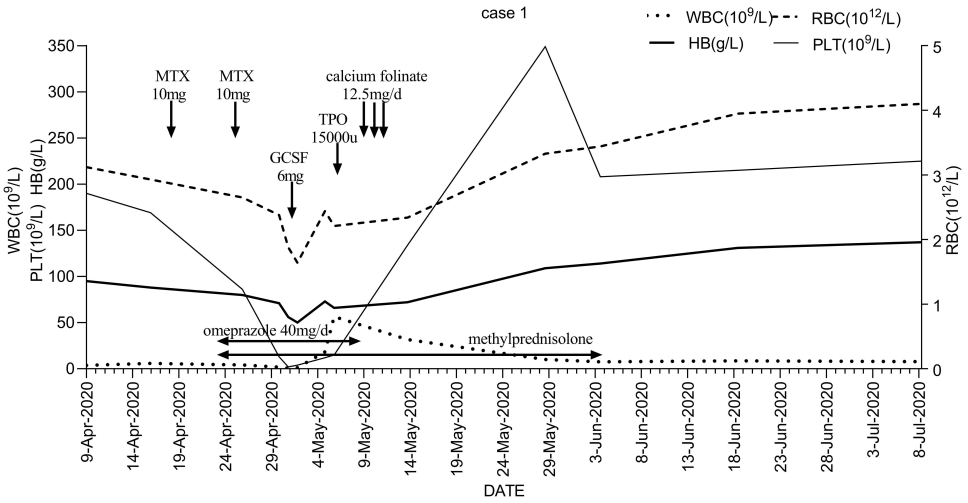

Figure 1 The change of blood cells in case 1 followed the use of omeprazole and methotrexate and the rescue of severe pancytopenia.

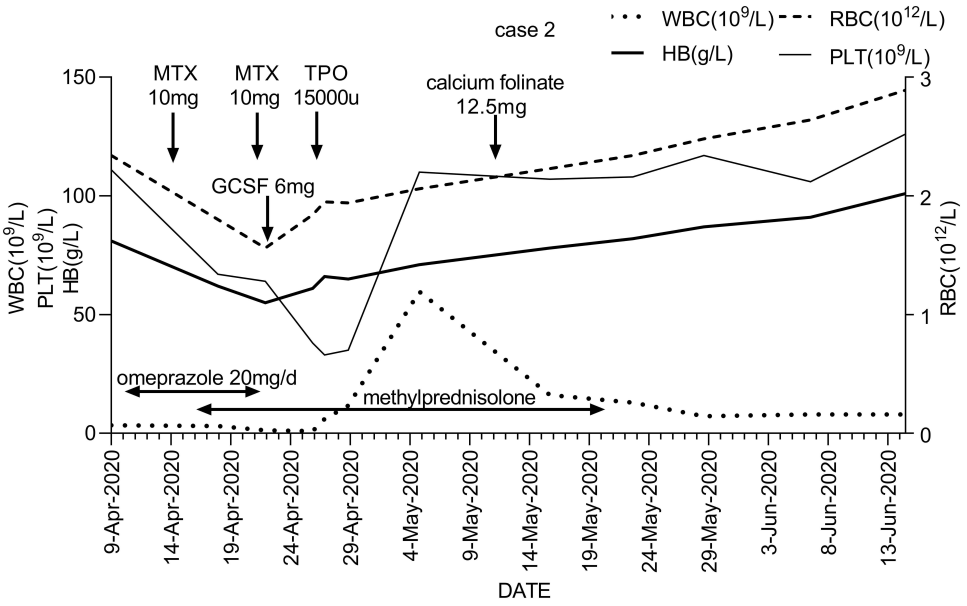

Figure 2 The change of blood cells in case 2 followed the use of omeprazole and methotrexate and the rescue of severe pancytopenia.

activity. We considered whether severe pancytopenia was a side effect of MTX, but the oral doses of MTX in the two cases were small. Even the second patient had been taking MTX without side effects such as pancytopenia, nausea, abdominal pain, deranged liver function tests and mouth ulcers for the past 20 years. Then drug-drug interactions was suspected. Owing to the same regimens including MTX and omeprazole, they were stopped immediately. And calcium folinate was taken to rescue the toxicity of methotrexate. Upon the procedure, their blood count returned to normal, which supported our hypothesis on the interactions between MTX and omeprazole.

Discussion

It has been reported that 95% of MTX is eliminated through renal excretion within 30h of administration.[1,8] Drug interactions between PPIs and MTX was first reported in 1993.[2] MTX and its metabolites 7-hydroxy-methotrexate are eliminated with distal renal tubules with hydrogen ions produced by the hydrogen/potassium ATPase pump in the renal tubules. PPIs inhibit renal elimination of the hydrogen ion, which may inhibit MTX and 7-hydroxy-methotrexate elimination.[3] PPIs could also inhibit methotrexate transport via human organic anion transporter 3 (hOAT3), which mediates the uptake of MTX at the basolateral side of renal proximal tubular cells.[2,4–6]

There is accumulating evidence to suggest that concomitant use of MTX (primarily at high doses) and PPIs such as omeprazole, esomeprazole, and pantoprazole may decrease MTX clearance.[9] Decreased clearance may result in elevated and prolonged serum levels of MTX and/or its metabolite hydroxymethotrexate, possibly leading to MTX toxicities. However, there is no evidence suggestive of increased risk for patients using a PPI in conjunction with low-dose MTX.[10] The two cases were assigned a Drug Interaction Probability Scale (DIPS) score to assess the likelihood that PPIs and low-dose MTX interaction are the cause of pancytopenia, with resultant rating of probable (score 7; Table S3).[10] We considered severe pancytopenia due to possible drug–drug interactions between low-dose MTX and PPIs. The limitations related to the first case was that the plasma concentration of methotrexate were monitored after the toxicity of methotrexate was rescued, but not the timing of the severe pancytopenia onset. The second case did not monitored her plasma concentration of methotrexate. Clinicians should consider risk of MTX toxicity when in combination of PPIs. We emphasize to pay attention to drug interactions even if kidney function is normal. It is worth noting that monitoring laboratory values carefully when a PPI be required and doing a full medication reconciliation to check PPIs prior to MTX therapy.

Data Sharing Statement

The original contributions presented in the study are included in the Supplementary Materials, further inquiries can be directed to the corresponding author.

Ethics Statement

Ethics Committee of The Third Affiliated Hospital of Baotou Medical College (Sinopharm North Hospital) participating in the project has conducted an initial review of the case report in accordance with relevant laws and regulations, the Declaration of Helsinki and other ethical principles, and believes that it complies with relevant laws and regulations, Agree with the contents of the case report of "Pancytopenia Due to Possible Drug-drug Interactions Between Low-dose Methotrexate and Proton Pump Inhibitors" and passed the review of the ethics committee.

The patients provided their written informed consent to participate in this study. Both patients gave written informed consent for use of their medical history and laboratory test reports in this paper.

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Bleyer WA. The clinical pharmacology of methotrexate: new applications of an old drug. *Cancer*. 1978;41:36–51. doi:10.1002/1097-0142(197801)41:1<36::AID-CNCR2820410108>3.0.CO;2-I

2. Reid T, Yuen A, Catolico M, Carlson RW. Impact of omeprazole on the plasma clearance of methotrexate. *Cancer Chemother Pharmacol*. 1993;33:82–84. doi:10.1007/BF00686028
3. Troger U, Stotzel B, Martens-Lobenhoffer J, Gollnick H, Meyer FP. Drug points: severe myalgia fran interaction between treatments with pantoprazole and methotrexate. *BMJ*. 2002;30(3):963–965.
4. Suzuki K, Doki K, Homma M, et al. Co-administration of proton pump inhibitors delays elimination of plasma methotrexate in high-dose methotrexate therapy. *Br J Clin Pharmacol*. 2009;67:44–49. doi:10.1111/j.1365-2125.2008.03303.x
5. Breedveld P, Zelcer N, Pluim D, et al. Mechanism of the pharmacokinetic interaction between methotrexate and benzimidazoles: potential role for breast cancer resistance protein in clinical drug-drug interactions. *Cancer Res*. 2004;64:5804–5811. doi:10.1158/0008-5472.CAN-03-4062
6. Chioukh R, Noel-Hudson MS, Ribes S, Fournier N, Becquemont L, Verstuyft C. Proton pump inhibitors inhibit methotrexate transport by renal basolateral organic anion transporter hOAT3. *Drug Metab Dispos*. 2014;42:2041–2048. doi:10.1124/dmd.114.058529
7. Reeves DJ, Moore ES, Bascom D, Rensing B. Retrospective evaluation of methotrexate elimination when co-administered with proton pump inhibitors. *Br J Clin Pharmacol*. 2014;78(3):565–571. doi:10.1111/bcp.12384
8. Boerrigter E, Crul M. A non-interventional retrospective cohort study of the interaction between methotrexate and proton pump inhibitors or aspirin. *Ann Pharm Fr*. 2017;6:2.
9. Naranjo C, Busto U, Sellers E, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30:239–245. doi:10.1038/clpt.1981.154
10. Hall J, Bolina M, Chatterley T, Jamali F. Interaction Between Low-Dose Methotrexate and Nonsteroidal Anti-inflammatory Drugs, Penicillins, and Proton Pump Inhibitors: a Narrative Review of the Literature. *Ann Pharmacother*. 2017;51(2):163–178. doi:10.1177/1060028016672035