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UTILIZATION OF METHOTREXATE & MONITORING OF HEPATOTOXICITY IN A PSORIASIS PATIENT

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ABSTRACT

Introduction: Methotrexate (MTX) induces hepatic fibrosis in psoriasis patients who take the medicine for a long period. Patients are currently monitored for MTX-induced hepatic fibrosis by performing a liver biopsy, which is risky and time-consuming for the patient, or by monitoring plasma procollagen type III amino peptide (PIIINP), which is unconvincing. **The objective** of this study was to find new non-invasive biomarkers that may be used to monitor psoriasis patients for MTX-induced **hepatic fibrosis** & **serum liver fibrosis test** (Hepascore & Fibrotest score) might predict the risk of adverse liver-related outcomes and mortality. **Methods**: A relevant article search was done using search terms like methotrexate ADR, clinical application on routine monitoring in clinical practice & Methotrexate used in psoriasis patients & Monitoring of hepatotoxicity in psoriasis patients (Drug-induced liver injury) on Google Scholar, PubMed, Medline, Cochrane library. **Results:** When MTX is combined with folic acid, its efficacy is reduced while its tolerance is increased. Because the incidence of hepatic fibrosis varies so widely in the literature, it is impossible to quantify the risk of hepatic fibrosis. Type 2 diabetes and obesity were found to be linked to a higher incidence of liver fibrosis. Hepatitis B and C, and alcohol usage, were linked to a slightly higher but non-significant incidence of liver fibrosis. The most widely validated approach for monitoring liver fibrosis was Procollagen III for detection of hepatic fibrosis dosage, which had a sensitivity of 77.3 percent and a specificity of 91.5 percent. **Conclusions:** As a conclusion, we believe that the chance of developing advanced hepatic fibrosis while taking methotrexate for psoriasis is low in low-risk people, and that methotrexate is not the cause of the increasing liver disease. Psoriatic patients are inclined to acquire NAFLD by nature, and even more so when risk factors are present, so all patients should be tested for risk factors and the presence of NAFLD before beginning treatment. Hepascore monitoring in long-term MTX users could be an effective management technique for detecting liver fibrosis progression. The link between a higher Hepascore and all-cause mortality needs to be investigated further.

KEYWORDS: Methotrexate, Hepatotoxicity, utilization, contraindication, adverse effect in a psoriasis patient.

INTRODUCTION

Methotrexate is the most commonly used conventional systemic medication in the treatment of psoriasis, and it is still considered a first-line treatment in moderate to severe cases, both in monotherapy and in combination with other drugs. Rather than clinical trials or controlled prospective studies, the evidence supporting the use of MTX in moderate to severe psoriasis is based on retrospective investigations and more than 50 years of clinical experience.[1] Even though there has been a lot of study on the use of MTX in psoriasis, there is still debate over the manner of administration (subcutaneous vs. oral), the initial dose and escalation, and the influence of folic acid supplements on tolerability. The biggest drawback of MTX therapy for psoriasis is hepatotoxicity. The incidence of liver toxicity, particularly liver fibrosis, varies substantially depending on the underlying risk factors. Although liver biopsy is the gold standard for finding histological abnormalities, it is limited in clinical use due to its invasive nature.[2]

Methotrexate is an antimetabolite derivative of folic acid. After oral administration, it is absorbed from the gastrointestinal system, with 30 to 90% bioavailability. Parenteral dosing of MTX may increase its bioavailability. After oral treatment, the maximum blood concentration is obtained in 1-2 hours, whereas intramuscular injection takes 30-60 minutes. Because the liver metabolizes only a small fraction of MTX (10%) and the kidney is the principal route of elimination, acute renal insufficiency demands dosage adjustments to reduce MTX toxicity.

Contraindication & Adverse effect of Methotrexate in psoriasis patients

(a) Because of the teratogenic effect of MTX, it should not be used during pregnancy.
(b) Acute leukopenia, anemia, or thrombocytopenia.

In some circumstances, MTX may not be an appropriate treatment for psoriasis. As a consequence, MTX should be avoided by patients who suffer from[3]: -

- An excessive alcohol intake is discouraged, with recommendations ranging from the outright prohibition to no more than two drinks per day to avoid liver damage.
- Active infectious disorders, particularly chronic infections like (HIV infection or active untreated tuberculosis)
- Kidneys are the predominant excretion route for MTX (85%)
- Diabetes mellitus
- Recently administered vaccination, particularly (live vaccines).
- Obesity, characterized as a BMI of 30 or higher

The most frequent early adverse effects of methotrexate are gastrointestinal symptoms including nausea (8 percent) and anorexia. Other adverse effects include abnormal liver function tests (LFTs) (25%) and hematological (11%) effects, as well as teratogenic, abortifacient, and pulmonary consequences (1 percent).[4]

Efficacy of Methotrexate

After non-steroidal anti-inflammatory medicines, methotrexate is one of the most widely utilized drugs in Psoriatic Arthritis. Methotrexate's substantial use in Psoriatic Arthritis is partially related to its proven efficacy in decreasing RA synovitis and improving psoriasis. The evidence for MTX's efficacy in Psoriatic Arthritis has been limited in clinical trials. Despite the lack of evidence, methotrexate remains the conventional DMARD of choice in Psoriatic Arthritis. The pharmacological activity of MTX interacts with DNA strands and suppresses the immune system, delaying the buildup of dead skin cells significantly. MTX is given orally in a single weekly dose or three doses separated by 12 hours. Concomitant supplementation with folic acid (a B vitamin) is also possible. Effects on the disease could be seen within a few weeks after starting treatment, as the condition of the skin begins to improve, with full improvement occurring in 2–3 months. To entirely clear the condition, possible persisting plaques may be treated with topical application of another specialized medicine or UVB/PUVA phototherapy. This is also indicated when the MTX dose needs to be reduced due to toxicity; it can also be used with other medications, such as a retinoid. As a result of possible damage to the hepatic and renal functions, as well as a decrease in the body's capacity to generate white and red blood cells and platelets, patients using MTX need to be closely monitored with chest X-rays, regular blood tests, or a liver biopsy for more definite results. It's also worth noting that the intracellular buildup of MTX and certain metabolites depletes the folate reserve. Adverse effect risk may be dose-dependent or vary depending on the route of administration (parenteral administration has a lower risk). However, caution should be exercised because doses less than 15 mg/week may be inefficient in terms of illness control.[5]

Methotrexate Therapy Toxicity

There has been a lot of research done on the adverse effects of MTX treatment in psoriasis and Psoriasis-Arthritis. Despite a good benefit-to-toxicity ratio when compared to other treatments and immunosuppressive medications used to treat these illnesses, up to 50% of patients have at least one adverse drug response during treatment, and up to 30% of patients on long-term therapy discontinue taking the drug.[6]

Methotrexate associated with hepatotoxicity

Long-term low-dose of methotrexate treatment is known to induce liver damage, which can vary from basic liver enzyme increase to fatty liver, fibrosis, and finally cirrhosis. Recently, it was shown that methotrexate-induced liver damage is clinically and histopathologically comparable to NAFLD (Non-Alcoholic Fatty Liver Disease) and that higher cumulative doses or the presence of risk factors increase the development of NASH (Non- alcoholic steatohepatitis). However, if patients are carefully chosen and monitored for the development of liver fibrosis and cirrhosis, which are neither common nor severe, methotrexate can be administered safely and successfully for long-term therapy.[7,8] Because conventional indicators for liver injury, such as plasma alanine aminotransferase (ALT), might transiently increase in individuals treated with MTX even without the incidence of liver injury, monitoring psoriasis patients for MTX-induced hepatic fibrosis is complicated. Less dangerous approaches, such as monitoring plasma procollagen type III amino peptide (PIIINP), are becoming more popular, but this marker isn't always accurate in predicting hepatic fibrosis in psoriasis patients.[9] As a result, research has concentrated on identifying new biomarkers for MTX-induced hepatic fibrosis, leading to the discovery of a variety of prospective plasma biomarkers such as tissue-inhibitor of metalloprotease-1 (TIMP-1), laminin, haptoglobin, and matrix metalloproteinase-1 (MMP-2).[10] In addition to plasma biomarkers, physical approaches such as the Fibroscan value and indirect multi-test algorithms such as the Fibrotest score <7.1 kPa (average normal value is 5.3 kPa). The fibrosis score is a metric that assesses the stiffness of the liver, which is a sign of scarring: -

- A fibrosis score of F0 to F1 (2 to 7 kPa) indicates that the liver has little or no scarring.
- F2 fibrosis score (7.5 to 10 kPa) fibrosis implies moderate scarring that has migrated outside of the liver.

- F3 fibrosis score (10 to 14 kPa) implies extensive scarring that has spread and disrupted normal blood flow.
- A fibrosis score of F4 (14 kPa or greater) indicates late-stage scarring or cirrhosis, with permanent scarring and irreparable damage.

The duration of MTX use and cumulative dose of MTX did not vary significantly between individuals with a Hepascore of <0.84 and those without a Hepascore of ≥0.84. The rate of MTX cessation due to a liver cause was higher in the Hepascore ≥0.84 group.[11] As a biomarker for hepatic fibrosis defined according to liver specificity and stability within various MTX treatment groups, the Fibroscan and serum PIIINP proved to be superior to the Hepascore and hyaluronic acid. Biomarkers in numerous body fluids, including urine, are increasingly being detected using proteomics techniques. Urinary biomarkers have the advantage of being a non-invasive way to follow patients regularly. The researchers wanted to see if urine proteins linked to MTX-induced hepatic fibrosis in psoriasis patients could be used as biomarkers. Multiple proteins associated with hepatic fibrosis were detected in the urine of psoriasis patients who had received a high cumulative dose of MTX, which could be utilized as prognostic biomarkers in future diagnostics.[12] Protease inhibitors were added to the urine samples and centrifuged for 10 minutes at 3000 g. To avoid several freeze/thaw cycles, the supernatant was aliquoted into 1.5 mL polypropylene tubes and stored at 80°C. Psoriasis patients were involved in the study and were separated into two groups depending on their MTX cumulative dose: low cumulative dose (1500 mg) and high cumulative dose (>1500 mg). Due to an unknown cumulative MTX dose, 5 urine individuals were removed from analysis after sample collection. As confounders of hepatic fibrosis and/or steatosis, we included the use of additional medications, a high body mass index (BMI), diabetes mellitus type 2, and alcohol intake.[13]

Drug-induced hepatic fibrosis and cirrhosis are dose-dependent in RA and psoriasis; late effects of MTX therapy are more common when certain risk factors are present. Psoriasis has been associated with diabetes, obesity, decreased renal function, alcohol consumption, and substantial pre-MTX alterations on liver biopsy.

The pathogenesis of MTX hepatotoxicity involves MTX-induced hepatic folate deficiency. Folate supplementation thus leads to a significant decrease in hepatotoxicity.[14]

Diagnostic Tests

Liver biopsies for monitoring liver functions test for patients on Methotrexate therapy

MTX monitoring in cutaneous psoriasis suggests that if there are identified risk factors for hepatic fibrosis, a baseline liver biopsy should be done at 2–4 months, followed by a cumulative dosage of 1–1.5 g of MTX. Liver enzymes and procollagen III amino peptide (PIIINP) are evaluated before therapy, and if baseline levels are elevated, fibroscan or a modification in medication is advised. Alanine aminotransferase (ALT) levels are tested one week after therapy begins, then every two weeks for the first two months, and finally every three months. PIIINP is tested every 6 months, and if levels are high when compared to baseline values, the testing is repeated within weeks. Unless you have a pretreatment PIIINP >8.0 g/L, three abnormalities PIIINP levels (>4.2 g/L) in 12 months, or if you have increased PIIINP levels above 8.0 g/L in two consecutive samples, you should get a liver biopsy. Liver biopsies performed on individual patients in the high cumulative MTX dose participants revealed Roenigk scores of I and II, which are not considered fibrosis. Most patients are unlikely to develop MTX-induced hepatic fibrosis, but those with greater urine concentrations of the proposed biomarkers could be at risk. If this is the case, ITIH4 and N-cadherin could be used as early indicators for fibrosis, as urinary concentrations were higher in the low cumulative MTX dose group. Individuals with established MTX-induced hepatic fibrosis, i.e., Roenigk score above III, should be included, and urinary concentrations of the proposed biomarkers should be measured in individual patients. The clinical implications of the Roenigk score areas following: -[15]

- Grade 1 or 2 findings are the most common in those who get a liver biopsy for MTX monitoring. There are no therapeutic modifications that need to be made.
- Grade 3A: maintain MTX treatment, although liver biopsy should be done more often (within 6 months, instead of a 1.5g cumulative dose)
- Methotrexate should be stopped in grades 3B and 4.

In addition, patients with elevated urine ITIH4 and N-cadherin concentrations should be monitored for hepatic fibrosis progression over time. In any case, the significance of ITIH4, N-cadherin, and the other discovered urine proteins as possible biomarkers predictive of MTX-induced hepatic fibrosis should be evaluated in a prospective trial in which psoriasis patients are followed from the beginning of their MTX treatment.

Risk factors for methotrexate (MTX)-induced liver toxicity[16]

• Metabolic syndrome (obesity, hyperlipidemia, hypertension, type 2 diabetes mellitus)
• Alcohol intake above recommended limits
• Hepatitis B and C
• Other hepatotoxic drugs such as non-steroidal anti-inflammatory drugs
• Haemochromatosis

Adverse events of liver biopsy

Abdominal pain within 2 hours after a liver biopsy was evident in all to varying extents. In 21 patients, this lasted for up to 24 hours. One patient had to be re-

admitted after a three-day stay due to a major adverse event. A repeat abdominal ultrasonography revealed a minor capsular hemorrhage that resolved without transfusion within 24 hours. According to dermatology rules, none of the 11 people with early mild fibrosis had their MTX terminated since their symptoms were not severe enough. Clinically and via LFT, they were followed upon. They were tracked using LFT, as well as PIIINP in the case of dermatology patients.[17]

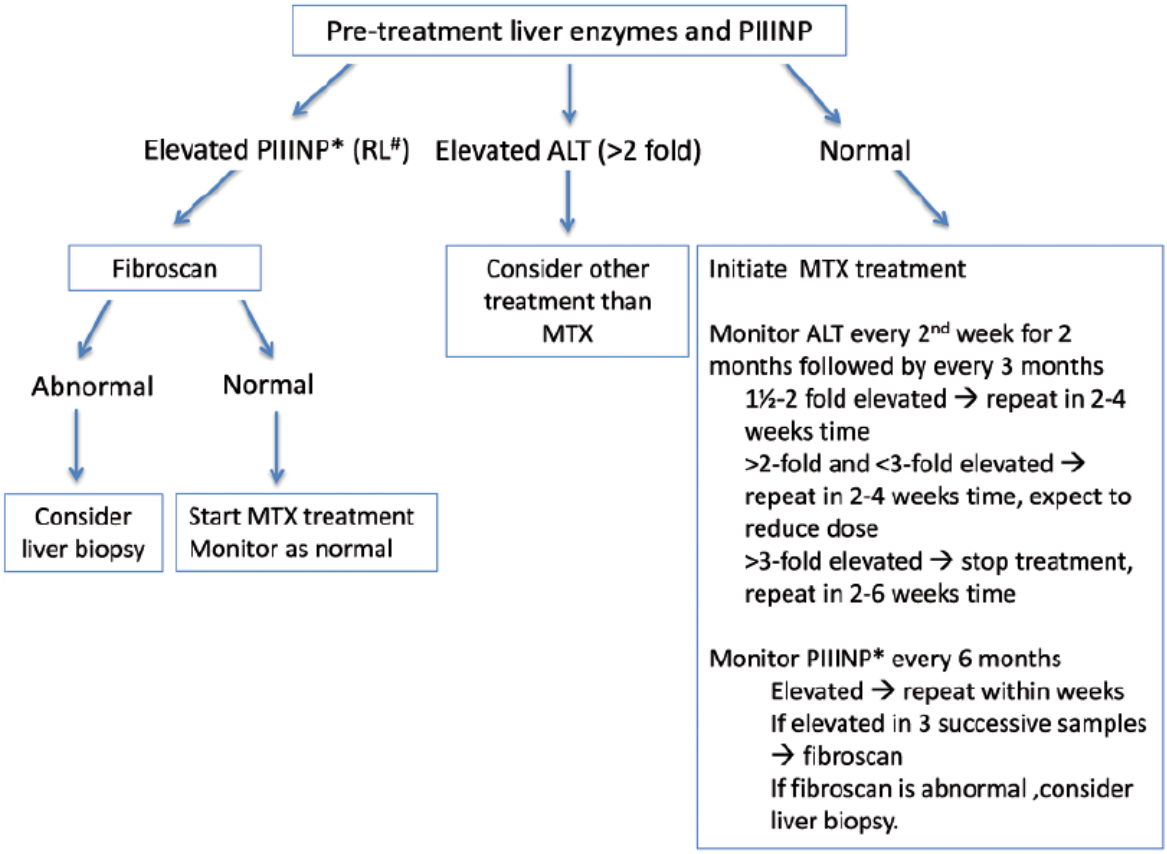

Fig 1: - Algorithm for methotrexate (MTX) treatment and monitoring of liver toxicity and fibrosis.[18]

Conclusion of Liver monitoring in psoriasis patients

Hepatotoxicity with MTX remains a clinical problem in psoriasis patients, and careful monitoring is necessary. The algorithm depicted in Fig. 1 is advised, and it is emphasized the necessity of recognizing the elevated risk of liver fibrosis in at-risk patient groups. Non-invasive monitoring of MTX liver damage is now possible because of new imaging techniques and biomarkers for liver fibrosis. These techniques will reduce the number of liver biopsies required during the follow-up of MTX patients. Based on their reported significance in hepatic fibrosis, the proteins found in urine samples of psoriasis patients who had received a high cumulative dose of MTX could be non-invasive biomarkers for MTX-induced liver impairment. To investigate the ability of the proposed biomarkers to predict MTX-induced hepatic fibrosis, researchers used patients with established MTX-induced hepatic fibrosis, several time points of sample collection, and synchronization with currently used methods to monitor disease progression.[19]

Prevention and Management of excessive Methotrexate

There are some factors of MTX-HD administration and post-treatment management that are consistent across all regimens to avoid MTX toxicity.

Maintaining adequate hydration: -To induce diuresis and prevent MTX intratubular precipitation, aggressive hydration is required. Most protocols suggest at least 2.5 to 3.5L/m2 of IV fluid hydration each day, beginning 4 to 12 hours before the MTX infusion begins.

Maintaining the pH of urine alkaline

When the pH of MTX and its metabolite 7-OH-MTX increases from 5 to 7, the solubility of MTX and its metabolite 7-OH-MTX, which is predominant with MTX-HD, increase by 20 and 12-fold, respectively. When the pH falls below 5.7, MTX and 7-OH-MTX precipitate in the renal tubules. In clinical practice, it is critical to start the MTX infusion only when the urine pH reaches 7.0 and to keep it there until plasma MTX levels drop below 0.1 μM.

Plasma Monitoring of Methotrexate concentration

Plasma MTX monitoring is an essential element of a high dose of methotrexate therapy. It aimed to determine patients who were at the greatest risk of MTX toxicity. The levels of MTX should be monitored daily. After initiating the MTX infusion, plasma MTX levels are routinely tested at 24, 48, and 72 hours. The initial MTX measurement for 24-hour infusion regimens may be at 36 hours. To minimize MTX toxicity, levels should be greater than 10 mg/mL after 24 hours, 1 mg/mL after 48 hours, and 0.15 mg/mL after 72 hours.[20]

Points of Monitoring parameters of Methotrexate therapy[21]

1) Before MTX therapy

- Complete blood cell counts
- Serum creatinine
- Liver function tests: ALT, AST
- Hepatitis B and C panel

2) During MTX therapy

- Repeat blood cell counts and kidney and liver function test every 4 to 8 weeks.

3) Contraindications to MTX therapy

- Pregnancy
- Alcoholism

Methotrexate-Related Therapeutic Combinations

Methotrexate in conjunction with UVB phototherapy in the narrowband spectrum

MTX in combination with narrowband UV-B phototherapy (NB-UV-B) (narrowband range from 311 to 312 nm) UVB phototherapy was formerly provided as a broadband source (290 to 320 nm) is more efficacious than NB-UV-B alone because it permits for dose and exposure reductions. Although the combination of MTX and NB-UV-B is theoretically associated with a higher risk of nonmelanoma skin cancer, the risk is lower than with MTX and psoralen plus UV-A. Long-term investigations, on either hand, are recommended.[22]

The use of MTX in conjunction with biologic therapy

To prevent the formation of anti-drug antibodies and/or to improve the pharmacokinetics of the biologic agent (2 + +/B), MTX can be given in combination with infliximab or adalimumab ineligible individuals.

Immunogenicity diminishes the therapeutic response to TNF inhibitors, especially infliximab and adalimumab. Antidrug antibodies reduce the efficacy of TNF blockers, according to a recent systematic study. Infliximab efficacy is improved by adding low dosages of MTX. In both psoriasis and psoriatic arthritis, adding MTX to an adalimumab regimen could enhance clinical outcomes. Combination therapy with etanercept and MTX has an acceptable safety profile and has been demonstrated to be more efficacious than etanercept alone in patients with moderate to severe psoriasis.[23]

MATERIALS AND METHODS

A relevant article search was done using search terms like methotrexate ADR, clinical application on routine monitoring in clinical practice & Methotrexate used in psoriasis patients & Monitoring of hepatotoxicity in psoriasis patients (Drug-induced liver injury) on Google Scholar, PubMed, Medline, Cochrane library. All of the articles were found and categorized as review articles, case studies, double-blind trials, and case reports. After reading the title and abstract, they were chosen and the complete text was reviewed to assess their content. In addition, we conducted a manual search of articles based on the references provided in the articles we discovered. After that, the data was evaluated and presented in a narrative format for each disorder that was utilized as a search parameter.

Each article was critically evaluated, and inclusion was determined by a consensus of both reviewers based on the relevance of the material to the topic. Following data extraction, material from the various subsections was processed and structured into this narrative evaluation.

RESULTS

Combining MTX with folic acid may reduce its efficacy while increasing its tolerability. The significant diversity in the incidence of hepatic fibrosis in the literature makes it impossible to quantify the risk of hepatic fibrosis. Type 2 diabetes and obesity were found to be linked to a higher incidence of liver fibrosis. Hepatitis B and C and alcohol usage were linked to a slightly higher but non-significant incidence of liver fibrosis. The most widely validated approach for monitoring liver fibrosis was Procollagen III for detection of hepatic fibrosis dosage, which had a sensitivity of 77.3 percent and a specificity of 91.5 percent. Depending on the prevalence of hepatic fibrosis, the Positive Predictive Value and Negative Predictive Value changed. The Fibrotest and Fibroscan have 83 and 50 percent sensitivities, respectively, with 61 and 88 percent specific characteristics. Abdominal pain within 2 hours after a liver biopsy was evident in all to varying extents. A repeat abdominal ultrasonography revealed a minor capsular hemorrhage that resolved without transfusion within 24 hours. According to dermatology rules, none of the 11 people with early mild fibrosis had their MTX terminated since their symptoms were not severe enough. Clinically and via LFT, they will be followed upon. They were tracked using LFT, as well as PIIINP in the case of dermatology patients.

CONCLUSION

As a conclusion, we believe that the chance of developing advanced hepatic fibrosis while taking methotrexate for psoriasis is low in low-risk people, and that methotrexate is not the cause of the increasing liver disease. Psoriatic patients are inclined to acquire NAFLD by nature, and even more so when risk factors are present, so all patients should be tested for risk factors and the presence of NAFLD before beginning treatment. The use of intensive monitoring with serial liver

biopsies, as advised by published recommendations, should be reconsidered. PIIINP levels can be a useful monitoring tool, but further research is needed before more solid recommendations can be made about using the PIIINP assay to replace liver biopsy in patients taking long-term methotrexate. Because MTX can induce a variety of side effects, some of which are life-threatening, it's critical to be aware of them so that the drug can be stopped and emergency measures are taken. Much close monitoring and adequate prevention can help prevent some of these adverse effects. Based on their reported significance in hepatic fibrosis, the proteins found in urine samples of psoriasis patients who had received a high cumulative dose of MTX could be non-invasive biomarkers for MTX-induced liver impairment. To investigate the ability of the proposed biomarkers to predict MTX-induced hepatic fibrosis, researchers used patients with established MTX-induced hepatic fibrosis, several time points of sample collection, and synchronization with currently used methods to monitor disease progression. Hepascore monitoring in long-term MTX users could be an effective management technique for detecting liver fibrosis progression. The link between a higher Hepascore and all-cause mortality needs to be investigated further.

CONFLICTS OF INTERESTS

No conflicts of interest.

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