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Review Article

The use of methotrexate in treatment of moderate to severe psoriasis

甲氨蝶呤對治療中度至嚴重的銀屑病的應用

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Psoriasis is a common, chronic and non-infectious skin disease characterised by well-defined erythematous plaques and papules with silvery scales and typical extensor distribution. It is a common skin disease which is sometimes refractory to treatment. Methotrexate, which was initially used to treat cancer, was discovered to be effective in clearing psoriasis in the 1950s. However, the use of methotrexate is associated with severe adverse reactions including acute haematologic toxicity and hepatotoxicity. Methotrexate should therefore be limited to patients with moderate to severe psoriasis and should not be prescribed to people who have had liver disease or preexisting blood dyscrasias. Careful selection of patients, pretreatment evaluation and close monitoring of patients after commencing methotrexate is essential. Laboratory tests should include regular complete blood count, renal and liver function tests, and liver biopsy after life cumulative dose of 1.0 to 1.5 g is reached. Moreover, folate is often added because it has been shown that folate supplementation during methotrexate therapy can alleviate both toxicity and adverse effects without jeopardising its efficacy.

銀屑病（牛皮癬）是一種常見的慢性非傳染皮膚病。銀屑病的特徵是皮膚表面齣現大小不等、具限分明的丘疹、紅班，表層覆蓋着銀白色鱗屑，常出現在伸肌的位置。銀屑病雖然普遍，然而治療過程漫長。甲氨蝶呤是用於治療癌症的藥物，在1950年代被發現對醫治銀屑病有顯著功效。可是，甲氨蝶呤有着嚴重的副作用，包括急性血液系統毒性和肝毒性。因此，甲氨蝶呤的使用應限制在中度至嚴重的病患者。患有肝病或血性惡液質的病人不應使用。嚴格挑選施藥病患者，治療前的評估，為進行甲氨蝶呤療程的病人作密切的監察都是必須的。功能檢測包括定時的全血細胞計數，腎及肝功能的測驗，以及為使用甲氨蝶呤累積劑量達1至1.5克的病人進行肝臟切片檢查。而在治療中加入服用葉酸能降低甲氨蝶呤所造成的不良副作用，同時亦能保持其療效。

Keywords: Adverse effects, folate, methotrexate, psoriasis

關鍵詞：不良副作用，葉酸，甲氨蝶呤，銀屑病

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Introduction and epidemiology

Psoriasis is a chronic recurrent disease affecting equally both sexes of any age. Population average prevalence between 1% and 3% is reported.[1] However, these prevalence figures are probably underestimated as these are mostly derived from surveys based on self-reporting.

In general, psoriasis is treated with a stepwise approach according to the severity of the disease or responsiveness to initial treatments. Topical preparations may be sufficient to control mild psoriasis, whereas phototherapy or systemic agents are usually required to achieve good control in patients with moderate to severe psoriasis. A survey conducted by the National Psoriasis Foundation found that a significant proportion of people with psoriasis were suffering from moderate to severe psoriasis.[2] There are various treatment options for moderate to severe psoriasis. However each carries its own risks and benefit. As there are no widely accepted standards for the treatment of moderate to severe psoriasis, the benefit and risks of phototherapy or systemic therapy must be balanced and discussed thoroughly with patient before embarking on these modalities. The treatment decisions may be influenced by the impact of regular and invasive monitoring of treatment-related toxicity. Expectation on the patient's lifetime cumulative exposure to these agents must be reckoned because psoriasis is a lifelong disease.

There were limited comparative clinical trials to accurately compare the efficacy of these therapies for moderate to severe psoriasis. Despite the scarcity of comparative trials, there is considerable clinical experience supporting the efficacy of methotrexate for moderate to severe psoriasis. This article briefly reviews the use of methotrexate for psoriasis, focusing on mechanism, recommended dosage, schedule and toxicity monitoring in the local context, drug interaction and the role of folate supplements. Safety concerns associated with methotrexate are also described.

Methotrexate, which was initially used to treat cancer, was discovered by Gubner to be effective in clearing psoriasis in patients being treated for carcinoma in the 1950s and was subsequently approved by the FDA in the 1970s.[3] It works by slowing down cell turnover and suppressing the immune system that is causing the skin inflammation. It is commonly used in patients with moderate to severe psoriasis because of its efficacy and convenience of oral administration. Furthermore, the drug has additional benefit in treating psoriatic arthritis and is effective in reducing the pain of psoriatic arthritis. However, the adverse effects of methotrexate are potential severe. Serious adverse effects include abnormal liver function tests, myelosuppression, and hepatic fibrosis. Furthermore, nausea and gastric discomfort is not uncommonly reported. Therefore, appropriate risk assessment is required to ensure proper selection of the appropriate candidates for methotrexate therapy.

Mechanisms of action of methotrexate

The mechanism of action of methotrexate is not fully understood. It is suggested that both the antifolate and immunosuppressive effects of methotrexate contribute to its therapeutic effect in psoriasis. Being structurally similar to folic acid, methotrexate, a 4-amino-10-methyl substituted derivative of folic acid, forms intracellular polyglutamates and inhibit the enzymes dihydrofolate reductase, thymidylate synthase, and glycinamide ribonucleotide transformylase, which are important in purine synthesis, thereby depleting the intracellular pool of reduced folate and creating a state of effective folate deficiency.[4] Through this mechanism, methotrexate interferes with DNA synthesis, repair, and hence cellular replication. Methotrexate also exerts its immunosuppressive effect by mechanisms that involve inhibition of T and B lymphocytes, suppression of proinflammatory cytokines, and inhibition of chemotaxis of neutrophils and monocytes.

Contraindications and drug interactions

The adverse effects of methotrexate can be categorised as minor or major as follows.

The most common minor adverse effects are stomatitis, malaise, nausea, vomiting, diarrhoea,

headache, mild alopecia, mood alteration, dizziness, fever, myalgia and polyarthralgia.[5] Many of these effects are associated with depletion of folate and therefore folate supplementation may alleviate these side effects. Despite the common occurrence, these side-effects are usually well tolerated by patients and are not life threatening. Often, these minor adverse effects are reduced by a decrease in methotrexate dose or an adjustment in the dosing schedule.

The major adverse effects include myelo-suppression, hepatic, renal and pulmonary disorders. These adverse effects occur infrequently but may be life threatening.[7] Therefore; timely evaluation of complete blood count, liver and renal function tests, periodic liver biopsy, and chest X-ray during therapy is recommended. Because of these serious adverse effects, methotrexate therapy is contraindicated in patients with significantly impaired renal or liver function, immunodeficiency, preexisting blood dyscrasias and those with known hypersensitivity or idiosyncratic reaction.[5]

Special precaution should be taken in patient of child bearing age. Methotrexate is contraindicated in pregnant women because it can cause fetal death or teratogenic effects.[5] Pregnancy should be avoided if either partner is on methotrexate. At least one ovulation cycle after discontinuation of methotrexate is recommended for female before contemplating conception. Female partners of male patients taking methotrexate should not conceive for at least 3 months after discontinuation of treatment.[6] Methotrexate is also contraindicated during breastfeeding due to the potential serious adverse effects in the infant.[5]

Methotrexate is also not recommended for people with active infectious disease or excessive alcohol consumption. Fortunately, most adverse events of methotrexate are reversible with early detection and respond to dose reduction or discontinuation.[5]

Co-administered drugs may influence methotrexate metabolism, interact with methotrexate and potentiate its toxicity. Non-steroidal anti-inflammatory drugs, salicylates, sulphonamides, chloramphenicol, phenothiazine, phenytoin and tetracyclines will increase the level of methotrexate whereas trimethoprim, sulphonamides and dapsone will enhance the risk of pancytopaenia.[5,7]

Particular caution is required for patients with psoriatic arthritis, who commonly use concomitant non-steroidal anti-inflammatory drugs for pain control.[7] They may be at increased risk for methotrexate-induced toxicity. This illustrates the importance of careful consideration of concomitant medication in psoriatic patients on methotrexate.

Role of folate supplement

Methotrexate, which is a folate antagonist, is a well established drug for many autoimmune and inflammatory diseases. However, it is also associated with significant adverse effects and toxicity. In patient with rheumatoid arthritis, folate supplementation is often used to reduce methotrexate-associated side effects and studies have demonstrated that folate supplementation during methotrexate therapy can alleviate both its toxicity and adverse effects without jeopardising its efficacy.[8] However, there was no randomised controlled trial regarding the use of folate supplement in psoriatic patient treated with methotrexate. In the absence of controlled trials, there is great variation in the indication for use and dosing regimens regarding folate supplementation for methotrexate treatment of psoriasis. Duhra demonstrated that folic acid supplement could reduce methotrexate-related gastrointestinal symptoms in psoriatic patients.[9]

There is much more experience on the use of folate supplement in patients with rheumatoid arthritis. Based on the studies of methotrexate therapy in patients with rheumatoid arthritis, Morgan and Stewart have shown that taking folic acid in doses of 1 to 5 mg daily could reduce nausea and other

side effects associated with methotrexate, and the timing of folic acid intake in relation to methotrexate did not influence its benefit in the reduction of these adverse effects.[10] However, further studies are required to provide similar evidence for choice of dose, frequency and timing of folate in psoriatic patients.

We recommend a daily dose of 5 mg of folic acid to reduce methotrexate adverse effect in our unit. Folinic acid should be considered if folic acid appears to be ineffective in reducing the adverse effects of methotrexate.

Monitoring during therapy and dosage recommendation[11,12]

Despite the benefit of methotrexate in treating psoriasis, patients treated with methotrexate may experience a range of acute and chronic adverse reactions including the more serious adverse effects like myelosuppression and liver toxicity. It is therefore recommended to perform regular and timely evaluation including complete blood picture (CBP), liver and renal function tests (LFT, RFT), and periodic liver biopsy during therapy.[11] Severe adverse effects such as significant liver derangement and myelosuppression preclude those affected patients from further treatment with methotrexate.

Before starting methotrexate, it is recommended to perform baseline investigations including CBP, LFT, RFT, urinalysis, creatinine clearance, hepatitis B serology and baseline chest X-ray.[13] Additional blood test like hepatitis C serology and HIV antibodies may also be considered in those patients with clinical indications. Lung function tests may be required in patients with a current or past history of severe respiratory disease.

In stable psoriasis vulgaris, methotrexate can be started with a weekly dose of 5.0-7.5 mg. In elderly and unstable psoriasis such as generalised pustular psoriasis or erythrodermic psoriasis, a testing dose of 2.5 mg should be started, which can then be increased to 7.5 mg weekly one week later, provided that CBP at that time is normal. Subsequent dosage should be titrated according to clinical response and patient's tolerability. The treatment schedule should be adjusted individually in order to achieve acceptable disease control at the lowest possible dose. The dosage should be increased at intervals of one to two weeks, up to 20 mg/week if the patient shows inadequate response.[14,15] A weekly dose of methotrexate is recommended because studies have shown that lower dosage given daily or on alternate days can result in a four-fold increased risk of hepatic fibrosis compared to larger doses given once weekly.[16]

In most patients, improvement can be observed within four to six weeks of using methotrexate. After commencement of methotrexate therapy, CBP should be monitor weekly for the first two weeks, every two weeks for one month and monthly thereafter. RFT should be checked every three months and LFT should be repeated every four to eight weeks. Folate supplement at 5 mg daily can be given to reduce some of the adverse effects of methotrexate. Not uncommonly, liver function derangement is noticed after commencement of methotrexate. For minor elevations in AST or ALT (2-fold increase or less), repeating LFT in 2-4 weeks until it becomes normalised is suggested. Repeat LFT in 2-4 weeks intervals is recommended for moderate and persistent elevations in AST or ALT (2-fold increase or more). Dosage reduction, discontinuation of methotrexate or liver biopsy is indicated as necessary in those patients who have moderate and persistent liver derangement.

There are various methods to assess methotrexate liver toxicity. Liver biochemistry is a simple test that is often used. However, because of its low sensitivity, regular liver biochemistry is not good enough to detect early methotrexate-induced hepatic fibrosis.[11,12] Liver biopsy is still considered the most reliable method of detecting hepatic fibrosis in patients treated with methotrexate.

It has been recommended that the first liver biopsy should be performed when a life cumulative methotrexate dose of 1.0-1.5 g is reached. Liver biopsy should be repeated at every additional cumulative dose of 0.5-1.5 g thereafter,[11] depending on the results of the initial liver biopsy histological grading until the cumulative dose of methotrexate is more than 4.0 g. By then, liver biopsy should be performed after each additional 0.5-1.0 g of methotrexate. The histology of liver biopsy will provide information on the risk of hepatic fibrosis and to gauge the risk of continuing use of methotrexate.[12] In patients with risk factors for liver damage like chronic alcohol intake, hepatitis B carrier,* diabetes mellitus, obesity, inheritable liver disease, history of exposure to hepatotoxins and persistent abnormal liver function tests, a better and safer alternative other than methotrexate should be considered. If methotrexate is the only option for these patients, a baseline liver biopsy is suggested and repeated liver biopsy should be done at a lower cumulative dose of 0.5 g-1.0 g.

The modified Roenigk classification, from I to IV, is commonly used to grade hepatic fibrosis. Grade I indicates fatty change, grade II indicates mild to moderate inflammation, grade IIIA represents mild fibrosis, grade IIIB represents moderate to severe fibrosis, and grade IV indicates cirrhosis.

Patients with modified Roenigk grade I or II histological changes can continue methotrexate. However, patients with grade IIIA changes can continue methotrexate therapy, provided that repeat liver biopsy will be performed after 6 months of further treatment. Methotrexate should be discontinued in patients with grade IIIB or grade IV changes.[11]

A summary of the modified Roenigk classification and recommendation of further actions are shown in the Table 1.

In general, methotrexate therapy is relatively well tolerated provided that there is careful patient selection, together with regular monitoring of adverse effects and drug interactions during therapy. The long term clinical efficacy and relative safety of methotrexate therapy remain impressive.

Future development

Methotrexate induced liver toxicity is not uncommon in psoriatic patient, particularly those

Table 1. Modified Roenigk classification and recommendations on methotrexate (MTX) treatment

Grade	Histology	Recommendation
I	Normal; mild fatty infiltration/nuclear variability/portal inflammation	Continue MTX
II	Moderate to severe fatty infiltration/nuclear variability/portal tract expansion or inflammation/necrosis	Continue MTX
IIIA	Mild fibrosis	May continue MTX therapy but need repeat liver biopsy after 6 months
IIIB	Moderate to severe fibrosis	Stop MTX
IV	Cirrhosis	Stop MTX

**There has been a recent paradigm shift in the management of people with chronic hepatitis B infection, joint consultation with the concerned specialists will be invaluable in making clinical decision in this scenario.*

linked to underlying liver problems. Hepatic fibrosis remains one of the most important adverse effects. Optimised clinical management of methotrexate-induced liver fibrosis requires precise definition of the stage of fibrogenic process, which is the main determinant of prognosis and therapeutic decisions. Liver biopsy remains the gold standard for assessment of hepatic fibrosis. However, regular liver biopsy is not only invasive, but is also costly and prone to sampling error. Complications of liver biopsy can be catastrophic albeit uncommonly seen. The mortality rate of liver biopsy is around 9/100,000,[17] commonly secondary to haemoperitoneum. Minor complications are more common. Pain after procedure and haematoma are the two most common minor complications and up to 30% of patient may experience pain of varying severity. Other rare minor complications include minor bleeding (6%), haemobilia (0.05%), puncture of other viscera (0.01-0.1%), sepsis and intrahepatic arteriovenous fistulae.

Many non-invasive markers of liver fibrosis have been assessed in the clinical setting as surrogate markers of early hepatic fibrosis. It seems that serum type III procollagen aminopeptide (PIIINP) is the most promising. Research has shown that patients with consistently normal PIIINP levels on serial follow up are at low risk of developing substantial liver fibrosis.[18,19] The Manchester protocol is developed by making use of PIIINP assays to predict liver fibrosis and to reduce the number of liver biopsies. This involves the measurement of PIIINP every three months. It has been suggested that liver biopsy is indicated if there is elevation of pretreatment PIIINP above 8.0 ug/L, persistent elevation of PIIINP above the normal range (1.7-4.2 ug/L) in at least three samples over a 12-month period or elevation of PIIINP above 8.0 ug/L in two consecutive samples. Methotrexate should be withdrawn if there is persistent elevation of PIIINP above 10.0 ug/L in at least 3 samples in one 12 month period. However, there are limitations in PIIINP monitoring, including the inability to detect preexisting liver damage, lack of organ specificity, and possible PIIINP elevation resulted from arthritis.[18] Therefore, it is still recommended to perform early liver biopsies for high-risk patients.

Based on available evidence, it can be anticipated that non-invasive markers of liver fibrosis will become a useful tool in early detection of methotrexate induced liver toxicity. However, their implementation is expected to reduce, but not to completely eliminate, the need for liver biopsy.

Conclusion

Methotrexate is one of the well-established drugs for the treatment of moderate to severe psoriasis. Careful selection of patients, pretreatment evaluation and post-treatment monitoring of methotrexate is essential because of its serious adverse effects. Folate is usually added to reduce the adverse effects of methotrexate. Liver biopsy remains the gold standard to detect methotrexate-related hepatic fibrosis and it is recommended in patients who have received a cumulative dose of 1.0-1.5 g. It is anticipated that non-invasive markers of liver fibrosis, like PIIINP, will become a useful tool in the detection of methotrexate-induced liver toxicity.

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