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15 February 2019

Ms Grace Horzitski
Coroner's Legal Counsel
Coroner's Court of Victoria
65 Kavanagh Street
SOUTHBANK VIC 3006

Dear Ms Horzitski,

RE: INVESTIGATION INTO THE DEATH OF IAN J GILBERT

We refer to your letter of 12 December 2018 in relation to Coroner Carlin's recommendations in the Finding into Death with Inquest of Ian J Gilbert ("**Inquest Findings**"), which contained follow-up requests to Pfizer for further information.

We note in your first question that you enquire as to the status of the information that is contained within the Product Information for Methoblastin® (methotrexate) ("**Product Information**"), and that it appears that the information you enquire of is "the information that confused Mr Gilbert's general practitioner."

Whilst Pfizer did not appear at the Inquest Hearing and thus does not have as much insight into the evidence adduced at the Inquest Hearing as you do, we note at paragraph 50 of the Inquest Findings that Dr Lim "consulted MIMS online", and at paragraph 51 that he conceded that he failed to read some parts of MIMS. That Dr Lim only consulted MIMS and only did so in a cursory manner is confirmed by Coroner Carlin at paragraphs 100 and 101 of the Inquest Findings. Finally, at paragraph 104, it is noted that it was submitted that Dr Lim was "misled by MIMS".

Accordingly, it is not readily apparent in the Inquest Findings that Dr Lim did consult the Product Information.

In any case, we also provide the following additional information in response to your questions. The daily dosing with rest period schedule is an alternative regimen used for patients who may tolerate smaller, more frequent doses better than a single weekly dose. Such a dosing schedule has shown significantly less nausea, vomiting, headache and fatigue when compared to patients receiving single weekly doses.[1]

In clinical practice, the single weekly dose and divided dosing regimen (i.e. a weekly dose administered over up to a 36-hour period) remain the most commonly used.[2, 3]

As stated in the Product Information current at the time in question, all schedules should be continually tailored to the individual patient taking into consideration any underlying hepatic and renal function. In elderly patients with rheumatoid arthritis or psoriasis, due to safety reasons, weekly doses rather than daily doses are recommended.[3]

Pfizer is committed to perform ongoing drug safety monitoring and the regular review and updating of safety information in the Product Information for all its licensed medicines, including Methoblastin® (methotrexate). Pfizer will take under consideration the Coroner's recommendation in the Inquest Findings, in the ongoing consultation with the Therapeutic Goods Administration in efforts to further improve patient safety in this regard.

Yours sincerely,

Melissa McGregor
Managing Director
Pfizer Australia and New Zealand

References:
1. Radmanesh M. et al. Weekly vs. daily administration of oral methotrexate (MTX) for generalized plaque psoriasis: a randomized controlled clinical trial. International Journal of Dermatology 2011, 50: 1291-1293.
2. Menting SP. Methotrexate Dosing Regimen for Plaque-type Psoriasis: A Systematic Review of the Use of Test-dose, Start-dose, Dosing Scheme, Dose Adjustments, Maximum Dose and Folic Acid Supplementation. Acta Dermato-Venereologica 2016; 96: 32-28.
3. Australian Product Information - Methoblastin® (Methotrexate) tablets.

PRODUCT INFORMATION

Methoblastin® tablets 2.5 mg and 10 mg

WARNINGS

Methotrexate must be used only by physicians experienced in antimetabolite chemotherapy, or in the case of non-oncological conditions, by a specialist physician.

Because of the possibility of fatal or severe toxic reactions the patient should be fully informed by the physician of the risks involved and should be under his constant supervision.

Deaths have been reported with the use of methotrexate.

In the treatment of psoriasis and rheumatoid arthritis, methotrexate should be restricted to severe, recalcitrant, disabling disease which is not adequately responsive to other forms of therapy, but only when the diagnosis has been established by biopsy and / or after appropriate consultation.

1. Methotrexate may produce marked depression of bone marrow, anaemia, aplastic anaemia, leucopenia, neutropenia, thrombocytopenia and bleeding.

2. Methotrexate may be hepatotoxic, particularly at high dosage or with prolonged therapy. Liver atrophy, necrosis, cirrhosis, fatty changes and periportal fibrosis have been reported. Since changes may occur without previous signs of gastrointestinal or haematological toxicity, it is imperative that hepatic function be determined prior to initiation of treatment and monitored regularly throughout therapy. Special caution is indicated in the presence of pre-existing liver damage or impaired hepatic function. Concomitant use of other drugs with hepatotoxic potential (including alcohol) should be avoided.

3. Malignant lymphomas, which may regress following withdrawal of methotrexate, may occur in patients receiving low-dose methotrexate and, thus, may not require cytotoxic treatment. Discontinue methotrexate first and, if the lymphoma does not regress, appropriate treatment should be instituted.

4. Potentially fatal opportunistic infections, especially *Pneumocystis jirovecii* pneumonia, may occur with methotrexate therapy.

5. Vaccination with a live vaccine in patients receiving chemotherapeutic agents may result in severe and fatal infections.

6. Methotrexate given concomitantly with radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis.

7. Use in pregnancy: Pregnancy category D.
   Methotrexate has caused fetal death and / or congenital abnormalities. Therefore, it is not recommended in women of childbearing potential unless there is appropriate medical evidence that the benefits can be expected to outweigh the considered risks. Pregnant psoriatic and rheumatoid arthritis patients should not receive methotrexate. Women of childbearing potential should not be started on methotrexate until

pregnancy is excluded and should be fully counselled on the serious risk to the fetus should they become pregnant while undergoing treatment.

8. Impaired renal function is usually a contraindication.

9. Diarrhoea and ulcerative stomatitis are frequent toxic effects and require interruption of therapy; otherwise, haemorrhage enteritis and death from intestinal perforation may occur.

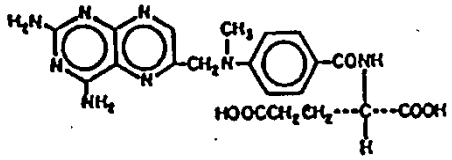
10. Unexpectedly severe (sometimes fatal) marrow suppression, aplastic anaemia and gastrointestinal toxicity have been reported with concomitant administration of methotrexate (usually in high doses) along with nonsteroidal anti-inflammatory agents (NSAIDs).

11. Methotrexate-induced lung disease including acute or chronic interstitial pneumonitis is a potentially dangerous lesion, which may occur acutely at any time during therapy and which has been reported at low doses. It is not always fully reversible and fatalities have been reported. Pulmonary symptoms (especially a dry, non-productive cough) may require interruption of treatment and careful investigation. Pulmonary lesions can occur at all dosages. Infections (including pneumonia) needs to be excluded. Patients should be closely monitored for pulmonary symptoms.

12. Both the physician and the pharmacist should emphasise to the patient the importance of the weekly dosing regimen: mistaken daily use may cause serious and sometimes life-threatening or fatal toxicity. For the same reason great care should be taken with dispensing to ensure the correct tablet strength of Methoblastin is given to the patient. Methoblastin is available as 2.5 mg and 10 mg tablets.

NAME OF THE MEDICINE

Methotrexate; CAS Registry Number is 59-05-2.



DESCRIPTION

Methotrexate is a yellow or orange crystalline powder. It is practically insoluble in water, in alcohol, and in methylene hydrochloride. It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides and carbonates.

Methoblastin tablets contain the active ingredient methotrexate.
Excipients: starch - maize, lactose, starch - pregelatinised maize, polysorbate 80, microcrystalline cellulose, magnesium stearate.

PHARMACOLOGY

Pharmacodynamics

Methotrexate has as its principal mechanism of action the competitive inhibition of the enzyme folic acid reductase. Folic acid must be reduced to tetrahydrofolic acid by this enzyme in the process of DNA synthesis and cellular replication. Methotrexate inhibits the reduction of folic acid and interferes with tissue cell reproduction. Methotrexate is a phase specific substance. Its main effect is directed to the S-phase of cell division. Actively proliferating tissues such as malignant cells, bone marrow, fetal cells, dermal epithelium, buccal and intestinal mucosa and cells of the urinary bladder are in general more sensitive to the effects of methotrexate. Cellular proliferation in malignant tissue is greater than in most normal tissue and thus methotrexate may impair malignant growth without irreversible damage to normal tissues.

In psoriasis, the rate of production of epithelial cells in the skin is greatly increased over that in normal skin. This differential in reproduction rates is the basis for the use of methotrexate to control the psoriatic process.

In patients with rheumatoid arthritis, effects of methotrexate on articular swelling and tenderness can be seen as early as three to six weeks. Although methotrexate clearly ameliorates symptoms of inflammation (pain, swelling, stiffness) there is no evidence that it induces remission of rheumatoid arthritis nor has a beneficial effect been demonstrated on bone erosions and other radiological changes which result in impaired joint use, functional disability and deformity. Most studies of methotrexate in patients with rheumatoid arthritis are relatively short term (three to six months). Data from long term studies indicate that an initial clinical improvement is maintained for at least two years with continued therapy.

Pharmacokinetics

Orally administered methotrexate is absorbed rapidly in most, but not all, patients and reaches peak serum levels within 1 to 2 hours.

Approximately one half of absorbed methotrexate is reversibly bound to serum protein, but exchanges with body fluids easily and diffuses into the body tissue cells. Elimination is triphasic. The first phase probably describes distribution into organs; the second, renal excretion; and the third, passing of methotrexate into the enterohepatic circulation. Excretion occurs mainly through the kidneys. Approximately 41% of the dose is excreted unchanged in the urine during the first six hours, 90% within 24 hours. Repeated daily doses result in more sustained serum levels and some retention of methotrexate over each 24 hour period which may result in accumulation of the drug within the tissues. The liver cells appear to retain certain amounts of the drug for prolonged periods even after a single therapeutic dose. Methotrexate is retained in the presence of impaired renal function and may increase rapidly in the serum and in the tissue cells under such conditions. Methotrexate does not penetrate the blood cerebrospinal fluid barrier in therapeutic amounts when given orally.

INDICATIONS

Antineoplastic Chemotherapy

Treatment of breast cancer, gestational choriocarcinoma and in patients with chorioadenoma destruens and hydatidiform mole. Palliation of acute and subacute lymphocytic leukaemia. Greatest effect has been observed in palliation of acute lymphoblastic (stem cell) leukaemias. In combination with corticosteroids, methotrexate may be used for induction of remission. The drug is now most commonly used for the maintenance of induced remissions. Methoblastin is also effective in the treatment of the advanced stages (III and IV, Peters Staging System) of lymphosarcoma, particularly in children and in advanced cases of mycosis fungoides.

Psoriasis Chemotherapy (See WARNINGS box and PRECAUTIONS)

Because of the high risk attending to its use, Methoblastin is only indicated in the symptomatic control of severe, recalcitrant, disabling psoriasis which is not adequately responsive to other forms of therapy, but only when the diagnosis has been established, as by biopsy and / or after dermatologic consultations.

Rheumatoid Arthritis Chemotherapy (See WARNINGS box and PRECAUTIONS)

Management of severe, recalcitrant, active rheumatoid arthritis in adults not responding to, or intolerant of, an adequate trial of NSAIDs and one or more disease modifying drugs. Aspirin, NSAIDs and / or low dose steroids may be continued, although the possibility of increased toxicity with concomitant use of NSAIDs including salicylate has not been fully explored (see PRECAUTIONS, INTERACTIONS WITH OTHER MEDICINES).

Steroids may be reduced gradually in patients who respond to methotrexate.

Combined use of methotrexate with gold, penicillamine, hydroxychloroquine, sulfasalazine or cytotoxic agents has not been studied and may increase the incidence of adverse effects. Rest and physiotherapy as indicated should be continued.

CONTRAINDICATIONS

Methotrexate should not be given to:

Pregnant women (see PRECAUTIONS, Use in Pregnancy).

Breast-feeding women (see PRECAUTIONS, Use in Lactation).

Patients with severe hepatic impairment.

Patients with severe renal impairment.

Patients with alcoholism or alcoholic liver disease.

Patients who have overt or laboratory evidence of immunodeficiency syndromes.

Patients with bone marrow depression or pre-existing blood dyscrasias, such as bone marrow hypoplasia, leucopenia, thrombocytopenia or anaemia.

Patients with severe, acute or chronic infections.

Patients with a known hypersensitivity to methotrexate or to any of the excipients.

Psoriasis and rheumatoid arthritis patients with peptic ulcer disease or ulcerative colitis.

During methotrexate therapy concurrent vaccination with live vaccines must not be carried out.

An increased risk of hepatitis has been reported to result from combined use of methotrexate and etretinate. Therefore, the combination of methotrexate with retinoids such as acitretin is also contraindicated.

PRECAUTIONS (See WARNINGS box)

Use with caution in the following circumstances

Methotrexate must be used only by physicians experienced in antimetabolite chemotherapy or, in the case of non-oncological conditions, by a specialist physician.

Because of the possibility of fatal or severe toxic reactions the patient should be fully informed by the physician of the risks involved before commencing methotrexate treatment, and should remain under the physician's constant supervision. Close monitoring for toxicity throughout treatment is mandatory, particularly in high dose therapy or where drug elimination could be impaired (renal impairment, pleural effusion, ascites).

Methotrexate exits slowly from the third-space compartments (e.g. pleural effusions or ascites) which results in a prolonged terminal phase half life and unexpected toxicity. In patients with significant third-space accumulation, it is advisable to evacuate the fluid before treatment and to monitor plasma methotrexate levels. Such patients require especially careful monitoring for toxicity, and require dose reduction, or in some cases, discontinuation of methotrexate administration (see PRECAUTIONS, Pulmonary).

Deaths have been reported with use of methotrexate in the treatment of malignancy and psoriasis.

In the treatment of psoriasis and rheumatoid arthritis, methotrexate should be restricted to severe, recalcitrant, disabling disease, which is not adequately responsive to other forms of therapy, but only when the diagnosis has been established, as by biopsy and / or after appropriate consultation.

Both the physician and the pharmacist should emphasise to the patient the importance of the weekly dosage regimens; mistaken daily use may cause serious and sometimes life-threatening or fatal toxicity (see WARNINGS box, PRECAUTIONS, Caution: Pharmacist, DOSAGE AND ADMINISTRATION and OVERDOSAGE). Great care should be taken to ensure the correct Methoblastin tablet strength is dispensed to the patient. Methoblastin is available as 2.5 mg and 10 mg tablets.

Methotrexate should be used with extreme caution in the presence of debility and in extreme youth or age (see PRECAUTIONS, Paediatric Use and PRECAUTIONS, Use in the Elderly).

Malignant lymphomas may occur in patients receiving low dose methotrexate, in which case therapy must be discontinued. These lymphomas may regress following withdrawal of methotrexate without requiring treatment. Failure of the lymphoma to show signs of spontaneous regression requires initiation of cytotoxic therapy.

Methotrexate, like other cytotoxic drugs, may trigger tumour lysis syndrome in patients with rapidly growing tumour.

Methotrexate has the potential for serious toxicity. Toxic effects may be related in frequency and severity to dose or frequency of administration, but have been seen at all doses. Because the toxic effects can occur at any time during therapy, it is necessary to follow the patients on methotrexate therapy very closely.

When such reactions do occur, the drug should be reduced in dosage or discontinued and appropriate corrective measures should be taken. If methotrexate therapy is reinstituted, it should be carried out with utmost caution, with adequate consideration of further need for the drug, and with increased alertness as to possible recurrence of toxicity.

If acute methotrexate toxicity occurs, patients may require folinic acid.

Adequate folinic acid (calcium folinate) protection is indicated in high-dose methotrexate therapy. The administration of calcium folinate, hydration, and urine alkalisation should be carried out with constant monitoring of the toxic effects and the elimination of methotrexate. Appropriate calcium folinate administration can be discontinued when the serum methotrexate concentration level is below 10^{-8} M (see OVERDOSAGE).

Folinic acid deficiency states may increase methotrexate toxicity.

Concomitant use of hepatotoxic or haematotoxic DMARDs (disease-modifying antirheumatic drugs, e.g. leflunomide) is not advisable.

Organ System Toxicity

Gastrointestinal

Methotrexate should be used with extreme caution in the presence of infection, peptic ulcer and ulcerative colitis.

Gastrointestinal disorders frequently require dosage adjustment. Vomiting, diarrhoea and ulcerative stomatitis are frequent toxic effects and require interruption of therapy; otherwise haemorrhagic enteritis and death from intestinal perforation may occur. Supportive therapy (including preventative dehydration) should be instituted.

In rare cases the effect of methotrexate on the intestinal mucosa has led to malabsorption or toxic megacolon.

Haematologic

Methotrexate may produce marked depression of bone marrow, anaemia, leucopenia, thrombocytopenia and bleeding. Clinical sequelae such as fever, infections, haemorrhage from various sites and septicaemia may be expected.

Methotrexate should not be used in patients with pre-existing haematopoietic impairment (see CONTRAINDICATIONS).

In patients with malignant disease who have pre-existing bone marrow aplasia, leucopenia, thrombocytopenia or anaemia, the drug should be used with caution, if at all.

Pretreatment and periodic haematologic studies are essential to the use of methotrexate in chemotherapy because of its common effect of haematopoietic suppression, manifesting as

anaemia, aplastic anaemia, pancytopenia, leucopenia, neutropenia and/or thrombocytopenia. This may occur abruptly and on apparent safe dosage, and any profound drop in blood cell count indicates immediate discontinuation and institution of appropriate therapy.

If profound leucopenia occurs during therapy, bacterial infection may occur or become a threat. Cessation of the drug and appropriate antibiotic therapy is usually indicated. In severe bone marrow depression, blood or platelet transfusions may be necessary.

In the treatment of neoplastic diseases, methotrexate should be continued only if the potential benefit outweighs the risk of severe myelosuppression.

Folate supplementation may permit continuation of methotrexate therapy with resolution of anaemia.

Concomitant administration of folate antagonists such as trimethoprim/sulphamethoxazole has been reported to cause an acute megaloblastic pancytopenia in rare instances (see INTERACTIONS WITH OTHER MEDICINES, Antibiotics, *Oral Antibiotics*).

Megaloblastic anaemia has also been reported, mainly in elderly patients receiving long-term weekly methotrexate therapy.

Hepatic

Methotrexate may cause acute and chronic hepatotoxicity, particularly at high dosage or with prolonged therapy, including liver atrophy, necrosis, hepatic cirrhosis, acute hepatitis, fatty changes and periportal fibrosis. Transient and asymptomatic liver enzyme elevations are frequently seen after methotrexate administration, and do not appear predictive of subsequent hepatic disease.

Particular attention should be given to the appearance of liver toxicity, since changes may occur without previous signs of gastrointestinal or haematologic toxicity. It is imperative that liver function be determined prior to initiation of treatment and monitored regularly throughout therapy (see PRECAUTIONS, Laboratory Monitoring, *Liver Function Tests*). Special caution is indicated in the presence of pre-existing liver damage or impaired hepatic function.

Methotrexate has caused reactivation of hepatitis B infection or worsening of hepatitis C infections, in some cases resulting in death. Some cases of hepatitis B reactivation have occurred after discontinuation of methotrexate. Clinical and laboratory evaluation should be performed to evaluate pre-existing liver disease in patients with prior hepatitis B or C infections. Based on these evaluations, treatment with methotrexate may not be appropriate for some patients.

The primary risk factors for severe liver damage, due to methotrexate hepatotoxicity, include: previous liver disease, repeatedly abnormal liver function tests, alcohol consumption/abuse, anamnestic hepatopathy (including chronic hepatitis B or C), and a family history of hepatopathy. Secondary risk factors for methotrexate hepatotoxicity include diabetes mellitus (in patients treated with insulin), obesity and exposure to hepatotoxic medicines or chemicals. Additional hepatotoxic medicinal products should not be taken during treatment with methotrexate unless clearly necessary and the consumption of alcohol should be avoided (see INTERACTIONS WITH OTHER MEDICINES).

In studies in psoriatic patients, hepatotoxicity appeared to be correlated not only to the cumulative dose of the drug but also to the presence of concurrent conditions such as alcoholism, obesity, diabetes, advanced age and arsenical compounds. Chronic toxicity is potentially fatal; it generally has occurred after prolonged use (generally 2 years or more) and after a total cumulative dose of at least 1.5 grams.

Liver biopsies are recommended for patients with elevated risk factors for hepatotoxicity or those that have received a cumulative dose of 1.0 g – 1.5 g of methotrexate (see PRECAUTIONS, Laboratory Monitoring, *Liver Function Tests*).

Musculoskeletal

Methotrexate given concomitantly with radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis.

Infection or Immunologic States

Any infections should be attended to before initiation of methotrexate therapy. Methotrexate should be used with extreme caution in the presence of active infections, and is usually contraindicated in patients with overt or laboratory evidence of immunodeficiency syndromes. Methotrexate therapy has immunosuppressive activity which can potentially lead to serious or even fatal infections. This factor must be taken into consideration in evaluating the use of the drug where immune responses in a patient may be important or essential.

Pneumonia (in some cases leading to respiratory failure) may occur. Potentially fatal opportunistic infections, especially *Pneumocystis jirovecii* pneumonia, may occur with methotrexate therapy. When a patient presents with pulmonary symptoms, the possibility of *Pneumocystis jirovecii* pneumonia should be considered.

Special attention should be paid in cases of inactive chronic infections (e.g. herpes zoster, tuberculosis, hepatitis B or C) because of their potential activation.

Immunisation

Methotrexate has some immunosuppressive activity and immunisation may be ineffective when given during methotrexate therapy. Immunisation with live virus vaccines is contraindicated during therapy (see CONTRAINDICATIONS). There have been reports of disseminated vaccinia infections after smallpox immunisation in patients receiving methotrexate therapy.

Pulmonary

Acute or chronic interstitial pneumonitis and pleural effusion, often associated with blood eosinophilia, may occur and deaths have been reported. Rheumatoid arthritis patients are at risk to develop rheumatoid lung disease, which is often associated with interstitial pulmonary disease. Methotrexate may exacerbate this underlying lung disease.

Pulmonary symptoms (especially a dry non-productive cough) or a non-specific pneumonitis occurring during methotrexate therapy may be indicative of a potentially dangerous lesion and require interruption of treatment and careful investigation. Although clinically variable, the typical patient with methotrexate-induced lung disease presents with fever, cough, chest pain, dyspnoea, hypoxaemia and an infiltrate on x-ray. This lesion can occur at all dosages. Infection (including pneumonia) needs to be excluded.

If methotrexate-induced lung disease is suspected, treatment with corticosteroids should be initiated and treatment with methotrexate should not be restarted.

Patients should be monitored for pulmonary signs and symptoms at each follow-up visit.

Renal

Methotrexate may cause renal damage that may lead to acute renal failure. Close attention should be given to renal function, including adequate hydration and urine alkalinisation. Measurement of serum methotrexate and renal function are recommended.

Methotrexate is excreted principally by the kidneys. Renal function should be closely monitored before, during and after methotrexate therapy. Impaired renal function may result in methotrexate accumulation of toxic amounts or even additional renal damage. Caution should be exercised if renal impairment is disclosed.

Drug dosage should be reduced or discontinued until renal function is improved or restored. A high fluid throughput and alkalinisation of the urine to pH 6.5 – 7.0 throughout therapy with methotrexate is recommended as a preventative measure (methotrexate is a weak acid and tends to precipitate at urine pH below 6.0).

Significant renal insufficiency is contraindicated for methotrexate therapy (see CONTRAINDICATIONS).

Concomitant use of proton pump inhibitors (PPIs) and high dose methotrexate should be avoided if possible and caution should be used in patients with renal impairment (see INTERACTIONS WITH OTHER MEDICINES).

Skin

Severe, occasionally fatal, dermatological reactions, including toxic epidermal necrolysis, Stevens-Johnson syndrome, exfoliative dermatitis, skin ulceration/necrosis and erythema multiforme have been reported in children and adults within days of methotrexate administration. Reactions were noted after single or multiple doses of methotrexate in patients with neoplastic and non-neoplastic diseases.

Burning and erythema may appear in psoriatic areas for 1 to 2 days following each dose. Lesions of psoriasis may be aggravated by concomitant exposure to ultraviolet radiation. Skin ulceration has been reported in psoriatic patients and a few cases of anaphylactoid reactions have been reported. Radiation dermatitis and sunburn may be "recalled" by the use of methotrexate.

Laboratory Monitoring

In general, the following laboratory tests are recommended as part of essential clinical evaluation and appropriate monitoring of patients chosen for or receiving methotrexate therapy; a complete blood count (with differential and platelet counts), haematocrit; urinalysis; renal function tests; hepatitis B or C infection testing and liver function tests. A chest X-ray is also recommended. The tests should be performed prior to therapy, at appropriate periods during therapy, and after termination of therapy. During initial or changing doses, or during periods of increased risk of elevated methotrexate blood levels (e.g. dehydration), more frequent monitoring may also be indicated.

During therapy for rheumatoid arthritis and psoriasis, monitoring of these parameters is recommended: haematology at least monthly, and liver and renal function every 1 to 2 months. More frequent monitoring is usually indicated during antineoplastic therapy. It may be important to perform liver biopsy or bone marrow aspiration studies where high dose or long term therapy is being followed.

Pulmonary Function Tests

Pulmonary function tests may be useful if lung disease (e.g. interstitial pneumonitis) is suspected, especially if baseline measurements are available (see PRECAUTIONS, Pulmonary).

Methotrexate Level

Serum methotrexate level monitoring can significantly reduce toxicity and mortality by allowing the adjustment of methotrexate dosing and the implementation of appropriate rescue measures.

Patients subject to the following conditions are predisposed to developing elevated or prolonged methotrexate levels and benefit from routine monitoring of levels: e.g., pleural effusion, ascites, gastrointestinal tract obstruction, previous cisplatin therapy, dehydration, aciduria, impaired renal function.

Some patients may have delayed methotrexate clearance in the absence of these features. It is important that patients be identified within 48 hours since methotrexate toxicity may not be reversible if adequate folinic acid rescue is delayed for more than 42 to 48 hours.

Monitoring of methotrexate concentrations should include determination of a methotrexate level at 24, 48, or 72 hours, and assessment of the rate of decline in methotrexate concentrations (to determine how long to continue folinic acid rescue).

Liver Function Tests / Liver Biopsy

Treatment should not be instituted or should be discontinued if any abnormalities of liver function tests, or liver biopsy, are present or develop during therapy. Such abnormalities should return to normal within two weeks after which treatment may be recommenced at the discretion of the physician.

Temporary increases in transaminases to twice or three times of the upper limit of normal have been reported by patients. In the case of a constant increase in liver-related enzyme, a reduction of the dose or discontinuation of therapy should be taken into consideration. Closer monitoring of liver enzymes is necessary especially in patients taking other hepatotoxic or haematotoxic medicinal products (e.g. leflunomide).

More frequent check-ups of liver function may become necessary during the initial phase of treatment, when the dose is increased and during episodes of a higher risk of elevated methotrexate blood levels (e.g. dehydration, impaired renal function, additional or elevated dose of medicines administered concomitantly, such as NSAIDs).

Repeated liver biopsies are recommended after a cumulative dose of 1.0 g – 1.5 g is achieved. Liver biopsies are also recommended for patients with elevated risk factors for hepatotoxicity (see PRECAUTIONS, Hepatic). Liver biopsy is also not necessary in the following cases: elderly patients, patients with an acute disease, patients with contraindication for liver biopsy

(e.g. cardiac instability, altered blood coagulation parameters) or patients with poor expectance of life.

Liver biopsy is recommended for patients during or shortly after initiation of therapy with methotrexate. Since a small percentage of patients discontinue therapy for various reasons after 2-4 months, the first biopsy can be delayed to a time after this initial phase. It should be performed when longer therapy can be assumed.

Liver biopsy after sustained use often shows histological changes, and fibrosis and cirrhosis have been reported; these latter lesions may not be preceded by symptoms or abnormal liver function tests in the psoriasis population. Periodic liver biopsies are usually recommended for psoriatic patients who are under long-term treatment.

Psoriasis

Liver damage and function tests, including serum albumin and prothrombin time, should be performed several times prior to dosing. Liver function tests are often normal in developing fibrosis or cirrhosis. These lesions may be detectable only by biopsy. It is recommended to obtain a liver biopsy at the following points: 1) before start of therapy or shortly after initiation of therapy (2 to 4 months); 2) after a total cumulative dose of 1.5 grams; and 3) after each additional 1.0 to 1.5 grams. In case of moderate fibrosis or any cirrhosis, discontinue the drug; mild fibrosis normally suggests a repeat biopsy in 6 months. Milder histologic findings such as fatty change and low grade portal inflammation are relatively common before the start of therapy. Although these mild changes are normally not a reason to avoid or discontinue methotrexate therapy, the drug should be used with caution.

Rheumatoid arthritis

Age at first use of methotrexate and duration of therapy have been reported as risk factors for hepatotoxicity. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in the rheumatoid population. Liver function tests should be performed at baseline and at 4 to 8 week intervals in patients receiving methotrexate for rheumatoid arthritis. Pretreatment liver biopsy should be performed for patients with a history of excessive alcohol consumption, persistently abnormal baseline liver function test values, or chronic hepatitis B or C infection. During therapy, liver biopsy should be performed if there are persistent liver function test abnormalities, or there is a decrease in serum albumin below the normal range (in the setting of well controlled rheumatoid arthritis).

If the results of a liver biopsy show mild changes (Roenigk grades I, II, IIIa), methotrexate may be continued and the patient monitored according to the recommendations listed above. Methotrexate should be discontinued in any patient who displays persistently abnormal liver function tests and refuses biopsy, or in any patient whose liver biopsy shows mild to severe changes (Roenigk grade IIIb or IV). When methotrexate is discontinued, a 'flare' of arthritis usually occurs within three to six weeks.

Information for Patients

Patients should be informed of the early signs and symptoms of toxicity, of the need to see their physician promptly if they occur, and the need for close follow-up, including periodic laboratory tests to monitor toxicity.

Patients should be informed that the dose of methotrexate is once weekly in the treatment of rheumatoid arthritis and psoriasis. The prescriber may specify the day of intake on the

prescription. Patients should be aware of the importance of adhering to the once weekly intake and that daily administration can lead to serious toxic effects.

Patients should be advised to report all symptoms or signs suggestive of infection.

Patients should be informed of the risk of pneumonitis and advised to contact their doctor immediately should they develop a persistent cough or dyspnoea.

Patients should be informed of the potential benefit and risk in the use of methotrexate. The risk of effects on reproduction should be discussed with both male and female patients taking methotrexate.

Patients receiving methotrexate should avoid excessive unprotected exposure to sun or sunlamps because of possible photosensitivity reactions.

Patients should be advised that adverse reactions to methotrexate, such as dizziness and fatigue, may affect their ability to drive or operate machinery.

Methoblastin tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Caution: Pharmacist

Because of its potential to cause severe toxicity, methotrexate therapy requires close supervision of the patient by the physician. Pharmacists should dispense no more than a seven day supply of the drug at one time. Refill of those prescriptions should be by direct order (written or oral) of the physician only.

Carcinogenicity

No controlled human data exist regarding the risk of neoplasia with methotrexate. Methotrexate has been evaluated in a number of animal studies for carcinogenic potential with inconclusive results.

Cytotoxic drugs have been reported to be associated with an increased risk of development of secondary tumours in humans. Reports of lymphoma, including reversible lymphomas and tumour lysis syndrome have been documented in patients treated with methotrexate.

Malignant lymphomas may occur in patients receiving low dose methotrexate, in which case therapy must be discontinued. Failure of the lymphoma to show signs of spontaneous regression requires initiation of cytotoxic therapy.

Assessment of the carcinogenic potential of methotrexate is complicated by conflicting evidence of an increased risk of certain tumours in rheumatoid arthritis. Benefit should be weighed against this potential risk before using methotrexate alone or in combination with other drugs, especially in children or young adults.

Genotoxicity

Methotrexate is mutagenic *in vivo* and *in vitro*. There is evidence that methotrexate causes chromosomal damage to animal somatic cells and human bone marrow cells. In vitro, methotrexate caused chromosomal aberrations in Chinese hamster A(T1) C1-3 cells, induced morphological transformation in mouse C3H/10$T_{1/2}$ clone 8 cells and was associated with an increased incidence of large colony mutants at the tk locus in L5178Y/tk$^{\pm}$ mouse lymphoma

cells. In vivo, it caused an increased incidence of polychromatic erythrocytes in mice and a transient and reversible increase in chromosomal aberrations in human bone marrow cells. The clinical significance of these findings is uncertain.

Methotrexate causes embryotoxicity, abortion and foetal defects in humans.

Effects on Fertility

Methotrexate has been reported to cause impairment of fertility, defective oogenesis or spermatogenesis, oligospermia, menstrual dysfunction and amenorrhoea in humans, during and for a short period after cessation of therapy.

Men treated with methotrexate should use contraception and not father a child during and for six months after treatment. Methotrexate may be genotoxic and has caused increased number of abnormal and immobile spermatozoa in clinical studies.

Since treatment with methotrexate can lead to severe and possibly irreversible disorders in spermatogenesis, men should seek advice about the possibility of sperm preservation before starting the therapy.

The possible risks of effects on reproduction should be discussed with patients of childbearing potential (see PRECAUTIONS, Use in Pregnancy).

Use in Pregnancy (Category D)

Use of methotrexate is contraindicated throughout pregnancy (see CONTRAINDICATIONS).

Methotrexate has been shown to be teratogenic. It has caused fetal death and / or congenital abnormalities in humans; therefore, it is not recommended in women of childbearing potential unless there is appropriate medical evidence that the benefits can be expected to outweigh the considered risks.

Women of childbearing potential should not be started on methotrexate until any existing pregnancy is excluded with certainty, e.g. pregnancy test prior to initiating therapy.

Both male and female patients should be fully counselled on the serious risk to the fetus should they become pregnant while undergoing treatment.

Pregnancy should be avoided and reliable effective contraception used if either partner is receiving methotrexate, during and for a minimum of six months after therapy has ceased, although the optimal time interval between the cessation of methotrexate treatment of either partner, and pregnancy, has not been clearly established.

Teratogenicity

There is evidence of a teratogenic risk in humans (craniofacial, cardiovascular and extremital malformations) and in several animal species.

Use in Lactation

Methotrexate passes into breast milk and is contraindicated during breastfeeding (see CONTRAINDICATIONS). The highest breast milk to plasma concentration ratio reached was 0.08:1. Because of the potential for serious adverse reactions from methotrexate in breast fed infants, it is contraindicated in nursing mothers.

Paediatric Use

Cases of overdose by miscalculation of dosage (particularly in juveniles) have occurred. Special attention must be given to dose calculation (see DOSAGE AND ADMINISTRATION).

Use in the Elderly

Due to diminished hepatic and renal functions as well as decreased folate states in elderly patients, relatively low doses should be considered and these patients should be closely monitored.

Fatal toxicities related to inadvertent daily rather than weekly dosing have been reported, particularly in elderly patients. It should be emphasised to the patient that the recommended dose is taken weekly for rheumatoid arthritis and psoriasis (see DOSAGE AND ADMINISTRATION).

Effects on Ability to Drive and Use Machines

Central nervous system symptoms, such as fatigue and dizziness, can occur during treatment with methotrexate which may have minor or moderate influence on the ability to drive and use machines.

INTERACTIONS WITH OTHER MEDICINES

Chemotherapeutic Agents

Enhancement of nephrotoxicity may be seen if high-dose methotrexate is administered in combination with a potentially nephrotoxic chemotherapeutic agent (e.g. cisplatin).

Asparaginase

The administration of asparaginase has been reported to antagonise the effect of methotrexate.

Mercaptopurine

Methotrexate increases the plasma levels of mercaptopurine. Combination of methotrexate and mercaptopurine may therefore require a dose adjustment.

Drug Highly Bound to Plasma Proteins

Methotrexate is bound in part to serum albumin after absorption and toxicity may be increased because of displacement by other highly bound drugs such as salicylates, sulphonamides, sulphonylureas, phenylbutazone, phenytoin, and some antibacterials such as penicillins, tetracycline, chloramphenicol, pristinamycin, probenecid and para-aminobenzoic acid. When methotrexate is used concurrently with these drugs, its toxicity may be increased.

Hypolipidaemic Compounds

Hypolipidaemic compounds such as cholestyramine proved preferential binding substrates compared to serum proteins when given in combination with methotrexate. These drugs, especially salicylates and sulphonamides, whether antibacterial, hypoglycaemic or diuretic, should not be given concurrently until the significance of these findings is established.

Probenecid and Drugs Reducing Tubular Secretion

Since probenecid and weak organic acids, such as "loop-diuretics", as well as pyrazoles reduce tubular secretion, great caution should be exercised when these medicinal products are coadministered with methotrexate.

Disease-Modifying Antirheumatic Drugs (DMARDs) and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs should not be administered prior to or concomitantly with high dose methotrexate, for example as used in the treatment of osteosarcoma. Concomitant administration of NSAIDs with high-dose methotrexate therapy has been reported to elevate and prolong serum methotrexate levels, resulting in deaths from severe haematological and gastrointestinal toxicity**.**

Caution should be used when NSAIDs and salicylates are administered concomitantly with lower doses of methotrexate. These drugs have been reported to reduce tubular secretion of methotrexate in an animal model and may enhance its toxicity.

Unexpectedly severe (sometimes fatal) marrow suppression and gastrointestinal toxicity have been reported with concomitant administration of methotrexate (usually in high doses) with some NSAIDs including aspirin and other salicylates, asapropazone, diclofenac, indomethacin and ketoprofen. Naproxen has been reported not to affect the pharmacokinetics of methotrexate but a fatal interaction has been reported.

Despite the potential interactions, studies of methotrexate in patients with rheumatoid arthritis have included concurrent use of dosage regimens of NSAIDs without apparent problems. However, doses used in rheumatoid arthritis (7.5 to 15 mg/week) are somewhat lower than those used in psoriasis. Larger doses could lead to unexpected toxicity. Therefore, until more is known about the NSAID/methotrexate interaction, it is recommended that methotrexate dosage be carefully controlled during treatment with NSAIDs.

The interactions of methotrexate and other antirheumatic drugs such as gold, penicillamine, hydroxychloroquine and sulfasalazine have not been studied. Concurrent use may increase the incidence of adverse effects.

Antibiotics

Ciprofloxacin

Renal tubular transport is diminished by ciprofloxacin; use of methotrexate with this drug should be carefully monitored.

Penicillins and Sulfonamides

Penicillins and sulfonamides may reduce renal clearance of methotrexate, thereby increasing serum concentrations of methotrexate. Haematologic and gastrointestinal toxicity have been observed in combination with high and low dose methotrexate. Use of methotrexate with penicillins and sulfonamides should be carefully monitored.

Oral Antibiotics

Oral antibiotics such as tetracycline, chloramphenicol and non-absorbable broad-spectrum antibiotics, may decrease intestinal absorption of methotrexate or interfere with the enterohepatic circulation by inhibiting bowel flora and suppressing metabolism of the drug by bacteria.

Trimethoprim/sulfamethoxazole has been reported rarely to increase bone marrow suppression in patients receiving methotrexate, probably by decreased tubular secretion and/or an additive anti-folate effect.

Concurrent use of the anti-protozoal pyrimethamine may increase the toxic effects of methotrexate because of an additive anti-folate effect.

Vitamins

Vitamin preparations containing folic acid or its derivatives may decrease responses to methotrexate and should not be given concomitantly. Folate deficiency states may increase methotrexate toxicity.

Other Cytotoxic Drugs

Methotrexate is often used in combination with other cytotoxic drugs. Additive toxicity may be expected in chemotherapy regimens which combine drugs with similar pharmacologic effects and special monitoring should be made with regard to bone marrow depression, renal, gastrointestinal and pulmonary toxicity. The dosage of methotrexate should be adjusted if it is used in combination with other chemotherapeutic agents with overlapping toxicities.

Hepatotoxic Agents

Concurrent use of other potentially hepatotoxic agents (e.g. leflunomide, sulfasalazine and alcohol) should be avoided due to an increased risk of hepatotoxicity. Special caution should be exercised when azathioprine is given concurrently with methotrexate. The combination of methotrexate with retinoids, such as acitretin, is contraindicated (see CONTRAINDICATIONS).

Leflunomide

Methotrexate in combination with leflunomide may also increase the risk of pancytopenia.

Nitrous Oxide Anaesthesia

The use of nitrous oxide anaesthesia potentiates the effect of methotrexate on folate metabolism, yielding severe unpredictable myelosuppression and stomatitis. This effect can be reduced by the use of folinic acid rescue.

Amiodarone

Amiodarone administration to patients receiving methotrexate treatment for psoriasis has induced ulcerative skin lesions.

Psoralen plus Ultraviolet Light (PUVA) Therapy

Skin cancer has been reported in a few patients with psoriasis or mycosis fungoides (a cutaneous T-cell lymphoma) receiving concomitant treatment with methotrexate plus PUVA therapy (methoxalen and ultraviolet light).

Packed Red Blood Cells

Care should be exercised whenever packed red blood cells and methotrexate are given concurrently. Patients receiving 24 hour methotrexate infusion and subsequent transfusions have showed enhanced toxicity probably resulting from prolonged serum-methotrexate concentrations.

Vaccines

Methotrexate is an immunosuppressant and may reduce immunological response to concurrent vaccination. Severe antigenic reactions may occur if a live vaccine is given concurrently.

Vaccination with a live vaccine in patients receiving chemotherapeutic agents may result in severe and fatal infections (see CONTRAINDICATIONS).

Theophylline

Methotrexate may decrease the clearance of theophylline; theophylline levels should be monitored when used concurrently with methotrexate.

Diuretics

Bone marrow suppression and decreased folate levels have been described in the concomitant administration of triamterene and methotrexate.

Proton Pump Inhibitors

Coadministration of proton pump inhibitors (e.g. omeprazole, pantoprazole) with methotrexate may decrease the clearance of methotrexate causing elevated methotrexate plasma levels with clinical signs and symptoms of methotrexate toxicity. Concomitant use of proton pump inhibitors and high dose methotrexate should be avoided if possible and caution should be used in patients with renal impairment.

Phenytoin

Cytotoxic agents may impair absorption of phenytoin, which may decrease efficacy of phenytoin and increase the risk for exacerbation of convulsions. Risk of toxicity enhancement or loss of efficacy of the cytotoxic drug due to increased hepatic metabolism by phenytoin is possible.

Cyclosporin

Cyclosporin may potentiate methotrexate efficacy and toxicity. There is a risk of excessive immunosuppression with risk of lymphoproliferation when the combination is used.

ADVERSE EFFECTS

The major toxic effects of methotrexate occur on normal, rapidly proliferating tissues, particularly the bone marrow and gastrointestinal tract. Ulcerations of the oral mucosa are usually the earliest signs of toxicity.

When adverse reactions do occur, the drug should be reduced in dosage or discontinued and appropriate corrective measures should be taken. This includes use of folinic acid (calcium folinate) (see PRECAUTIONS, General and OVERDOSAGE).

The most common adverse reactions of methotrexate are bone marrow suppression and mucosal damage which manifest as ulcerative stomatitis, leucopenia, nausea and other gastrointestinal disorders. Other reported adverse reactions include malaise, undue fatigue, chills and fever, headache, dizziness, drowsiness, tinnitus, blurred vision, eye discomfort and decreased resistance to infections.

In general, the incidence and severity of side effects are related to dose, dosing frequency, method of administration and duration of exposure. Adverse reactions are most common when using high and repeated doses of methotrexate in the treatment of malignant neoplasms.

Adverse reactions as reported for the various organ systems are as follows:

Immune System Disorders: Anaphylactoid reaction, anaphylactic reaction, hypogammaglobulinaemia.

Skin and Subcutaneous Tissue Disorders: Toxic epidermal necrolysis (Lyell's syndrome), Stevens-Johnson syndrome, exfoliative dermatitis, painful damage to psoriatic lesions, skin ulceration, skin necrosis, erythema multiforme, drug reaction with eosinophilia and systemic symptoms, dermatitis, erythematous rashes, pruritus, urticaria, photosensitivity, pigmentation disorder (depigmentation / hyperpigmentation), alopecia, petechiae, ecchymosis, telangiectasia, acne, folliculitis, furunculosis, nail changes.

Blood and Lymphatic System Disorders: Bone marrow depression, leucopenia, neutropenia, thrombocytopenia, anaemia, aplastic anaemia, megoblastic anaemia, eosinophilia, pancytopenia, agranulocytosis, lymphadenopathy, lymphoproliferative disorders, haemorrhage (from various sites).

Gastrointestinal Disorders: Mucositis, gingivitis, stomatitis, glossitis, anorexia, nausea, vomiting, diarrhoea, abdominal distress, haematemesis, melaena, gastrointestinal ulceration and bleeding, pancreatitis, intestinal perforation, noninfectious peritonitis, toxic megacolon, malabsorption, enteritis.

Hepatobiliary Disorders: Hepatic failure, acute and chronic hepatotoxicity, acute liver atrophy, necrosis, fatty metamorphosis, acute hepatitis, periportal fibrosis, hepatic cirrhosis, elevated liver enzymes, increase of transaminases and blood lactate dehydrogenase, decreased serum albumin. Alteration of liver function tests (increases in transaminases and LDH levels) is commonly reported but usually resolves within one month after cessation of therapy.

Renal and Urinary Disorders: Renal failure, severe nephropathy, dysuria, azotaemia, cystitis, haematuria, proteinuria, urogenital dysfunction.

Pregnancy, Puerperium and Perinatal Conditions: Abortion, fetal defects, fetal death

Reproductive System Disorders: Defective oogenesis or spermatogenesis, transient oligospermia, menstrual dysfunction, infertility**,** vaginal bleeding, vaginal ulceration, vaginitis, vaginal discharge, gynaecomastia, loss of libido, impotence.

Cardiac Disorders: Pericarditis, pericardial effusion.

Vascular Disorders: Vasculitis, hypotension, thromboembolic events (including arterial thrombosis, cerebral thrombosis, deep vein thrombosis, retinal vein thrombosis thrombophlebitis and pulmonary embolism).

Nervous System Disorders: Paraesthesia, headaches, dizziness, drowsiness, convulsions, aphasia, hemiparesis, speech impairment, paresis, dysarthria, lethargy, motor dysfunction, cranial nerve palsies, leucoencephalopathy, encephalopathy, CSF pressure increased, neurotoxicity, arachnoiditis, coma, paraplegia, stupor, ataxia, dementia, unusual cranial sensations.

Psychiatric Disorders: Depression, confusion, irritability, transient subtle cognitive dysfunction, mood alteration.

Respiratory, Thoracic and Mediastinal Disorders: Pneumonitis, interstitial pneumonitis deaths, interstitial pulmonary fibrosis, reversible eosinophilic pulmonary infiltrates chronic interstitial obstructive pulmonary disease, pharyngitis, alveolitis, pleural effusion, pleurisy, dyspnoea, chest pain, hypoxia, cough (especially dry and non-productive).

Eye Disorders: Conjunctivitis, blurred vision, eye discomfort, serious visual changes of unknown aetiology including transient blindness.

Ear and Labyrinth Disorders: Tinnitus.

Infections and Infestations: Infections (including fatal sepsis), decreased resistance to infection, opportunistic infections (sometimes fatal in patients receiving methotrexate therapy for neoplastic and non-neoplastic diseases). *Pneumocystis jirovecii,* pneumonia (most common infection), respiratory tract infection, cutaneous bacterial infections, pneumonia, sepsis, nocardiosis, histoplasmosis, cryptococcosis, herpes zoster, herpes simplex hepatitis, disseminated herpes simplex cytomegalovirus infection (including cytomegaloviral pneumonia), reactivation of hepatitis B infection, worsening of hepatitis C infection.

Neoplasms Benign, Malignant, and Unspecified (including Cysts and Polyps): Lymphoma (including reversible lymphoma), tumour lysis syndrome.

Metabolism and Nutrition Disorders: Diabetes mellitus, metabolic disorder.

Musculoskeletal, Connective Tissue and Bone Disorders: Osteoporosis, osteonecrosis (aseptic necrosis of the femoral head), soft tissue necrosis, abnormal tissue cell changes, arthralgia/myalgia, stress fracture.

General Disorders and Administration Site Conditions: Sudden death, increased rheumatoid nodules, pyrexia, chills, malaise, fatigue.

DOSAGE AND ADMINISTRATION

Because of its potential to cause severe toxicity, methotrexate therapy requires close supervision with particular caution to distinguish between daily and weekly dosage regimens. Weekly dosage prescriptions should specify a particular day of the week.

Antineoplastic Chemotherapy

Oral administration in tablet form is often preferred since absorption is rapid and effective serum levels are obtained.

For conversion of mg/kg bodyweight to mg/m^2 of body surface area or the reverse, a ratio of 1:30 is given as a guideline. The conversion factor varies between 1:20 and 1:40 depending on age and body build.

Breast Carcinoma

Prolonged cyclic combination chemotherapy with cyclophosphamide, methotrexate and fluorouracil has given good results when used as adjuvant treatment to radical mastectomy in primary breast cancer with positive axillary lymph nodes.

Choriocarcinoma and similar Trophoblastic Diseases

Methotrexate is administered orally in doses of 15-30 mg daily for a five day course. Such courses are usually repeated three to five times as required with a rest period of one or more weeks interposed between courses, until any manifesting toxic symptoms subside. The effectiveness of therapy is ordinarily evaluated by 24 hour quantitative analysis of urinary chorionic gonadotrophin hormone (βHCG), which should return to normal or less than 50 units/24 hour usually after the 3rd or 4th course and usually followed by a complete resolution of measurable lesions in 4 to 6 weeks. One to two courses of methotrexate after normalisation of βHCG is usually recommended. Before each course of the drug, careful clinical assessment is essential. Cyclic combination therapy of methotrexate with other antitumour drugs has been reported as being useful. Since hydatidiform mole may precede or be followed by choriocarcinoma, prophylactic chemotherapy with methotrexate has been recommended. Chorioadenoma destruens is considered to be an invasive form of hydatidiform mole. Methotrexate is administered in these disease states in doses similar to those recommended for choriocarcinoma.

Leukaemia

Acute lymphatic (lymphoblastic) leukaemia in children and young adolescents is the most responsive to present day chemotherapy. In young adults and older patients, clinical remission is more difficult to obtain and early relapse is more common. In chronic lymphatic leukaemia, the prognosis for adequate response is less encouraging. Methotrexate alone or in combination with steroids was used initially for induction of remission of lymphoblastic leukaemias. More recently, corticosteroid therapy in combination with other antileukaemic drugs or in cyclic combination therapy including methotrexate, has produced rapid and effective remissions.

Methotrexate alone, or in combination with other agents**,** appears to be the drug of choice for securing maintenance of drug induced remissions. When remission is achieved and supportive care has produced general clinical improvement, maintenance therapy is initiated, by administering methotrexate 2 times weekly in doses of 30 mg/m^2. If and when relapse does occur, reinduction of remission can again usually be obtained by repeating the initial induction regimen.

Lymphomas

In Burkitt's tumour, stages I-II, methotrexate has produced prolonged remission in some cases. Recommended dosage is 10 to 25 mg per day orally for 4 to 8 days. In stage III, methotrexate is commonly given concomitantly with other antitumour agents. Treatment in all stages usually consists of several courses of the drug interposed with 7 to 10 day rest periods.

Lymphosarcomas in stage III may respond to combined drug therapy with methotrexate given in doses of 0.625 mg to 2.5 mg/kg daily. Hodgkin's Disease responds poorly to methotrexate and to most types of chemotherapy.

Mycosis Fungoides

Therapy with methotrexate appears to produce clinical remissions in one half of the cases treated. Dosage is usually 2.5 to 10 mg daily by mouth for weeks or months. Dose levels of drug and adjustment of dose regimen by reduction or cessation of drug are guided by patient response and haematologic monitoring.

Psoriasis Chemotherapy

The patient should be fully informed of the risks involved and should be under constant supervision of the physician.

Assessment of renal function, liver function and blood elements should be made by history, physical examination and laboratory tests (such as full blood count, urinalysis, serum creatinine, liver function studies and liver biopsy if indicated) before beginning methotrexate, periodically during methotrexate therapy and before reinstituting methotrexate therapy after a rest period. Appropriate steps should be taken to avoid conception during and for at least twelve weeks following methotrexate therapy.

There are three commonly used general types of dosage schedules:

(1) weekly oral large doses

(2) divided dose intermittent oral schedule over a 36 hour period

(3) daily oral with a rest period.

All schedules should be continually tailored to the individual patient. Dose schedules cited below pertain to an average 70 kg adult. An initial test dose one week prior to initiation of therapy is recommended to detect any idiosyncrasy.

Recommended Starting Dose Schedules

1. Weekly single oral dose schedules: 10 – 25 mg per week until adequate response is achieved. With this dosage schedule, 50 mg per week should ordinarily not be exceeded.

2. Divided oral dose schedule: 2.5 mg at 12 hour intervals for three doses or at 8 hour intervals for four doses, each week. With this dosage, 30 mg per week should not be exceeded.

3. Daily oral dose schedule: 2.5 mg daily for five days followed by at least a two day rest period. With this dosage schedule, 6.25 mg per day should not be exceeded.

Dosage in each schedule may be gradually adjusted to achieve optimal clinical response, but not to exceed the maximum stated for each schedule. Once optimal clinical response has been achieved each dosage schedule should be reduced to the lowest possible amount of drug and to the longest possible rest period. The use of methotrexate may permit the return to conventional topical therapy, which should be encouraged.

Rheumatoid Arthritis Chemotherapy

The patient should be fully informed of the risks involved and should be under constant supervision by the physician.

Assessment of haematological, hepatic, renal and pulmonary function should be made by history, physician examination and laboratory tests before beginning, periodically during and before reinstituting methotrexate therapy. Appropriate steps should be taken in men and women to avoid conception during methotrexate therapy.

Both the physician and the pharmacist should emphasise to the patient the importance of the weekly dosage regimens: mistaken daily use may cause serious and sometimes life-threatening or fatal toxicity.

All schedules should be continually tailored to the individual patient. An initial test dose may be given prior to the regular dosing schedule to detect any extreme sensitivity to adverse effects. Complete blood count with platelets should be evaluated seven to ten days later.

Recommended starting dosage schedules are single oral doses of 7.5 mg once weekly, or divided oral doses of 2.5 mg at 12 hour intervals for three doses given as a course once weekly.

Therapeutic response usually begins within three to six weeks and the patient may continue to improve for another 12 weeks or more. The dosage in each schedule may be increased to 15 mg/week after six weeks in nonresponsive patients. If necessary, dosage may be gradually increased further to achieve optimal response, but not ordinarily to exceed a total weekly dosage of 20 mg. Once response has been achieved, each schedule should be reduced, if possible, to the lowest possible amount of drug and with the longest possible rest period.

The optimal duration of therapy is unknown. Limited data available from long-term studies indicate that the initial clinical improvement is maintained for at least two years with continued therapy. When methotrexate is discontinued, the arthritis usually worsens within three to six weeks.

Patients with Renal Impairment

Methotrexate is excreted primarily by the kidneys. In patients with renal impairment the dose may need to be adjusted to prevent accumulation of drug (see PRECAUTIONS, Organ System Toxicity, *Renal*).

Incompatibilities

Methotrexate has been reported to be incompatible with cytarabine, fluorouracil and prednisolone.

Instructions for Handling

Individuals who have contact with anti-cancer drugs or work in areas where these drugs are used may be exposed to these agents in air or through direct contact with contaminated objects.

Guidelines and procedures for appropriate handling and disposal of hazardous chemicals should be observed in the handling of cytostatics.

Pregnant staff should be excluded from working with this drug.

OVERDOSAGE

Cases of overdose, sometimes fatal, due to erroneous daily intake instead of weekly intake of oral methotrexate have been reported (see WARNINGS box and PRECAUTIONS).

Signs and Symptoms

Symptoms commonly reported following oral overdose include those symptoms and signs reported at pharmacological doses, particularly haematological and gastrointestinal reactions. These signs and symptoms include leucopenia, thrombocytopenia, anaemia, pancytopenia, bone marrow suppression, mucositis, stomatitis, oral ulceration, nausea, vomiting, gastrointestinal ulceration, gastrointestinal bleeding, anorexia, progressive weight loss and bloody diarrhoea. In some cases of overdose, no symptoms were reported. There have been

reports of death following overdose. In these cases, events such as sepsis or septic shock, renal failure and aplastic anaemia were also reported.

Treatment of Overdosage

Consider administration of activated charcoal in the event of a potentially toxic ingestion. Activated charcoal is most effective when administered within 1-hour of ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via nasogastric tube once the airway is protected.

Folinic acid (calcium folinate) neutralises effectively the immediate toxic effects of methotrexate. After an inadvertent overdosage of methotrexate, calcium folinate should be given as soon as possible and preferably started within 1 hour after the administration of methotrexate. As the time interval between methotrexate administration and folinic acid initiation increases, the effectiveness of folinic acid in counteracting toxicity decreases. Monitoring of the serum methotrexate concentration is essential in determining the optimal dose and duration of treatment with folinic acid.

Calcium folinate should be given at 10 mg/m^2 IV or IM q 6 hours until the serum methotrexate levels are below 10^{-8}M. In the presence of gastric stasis or obstruction leucovorin should be administered parenterally. Concomitant hydration (3 L/d) and urinary alkalinisation with sodium bicarbonate should be employed. The bicarbonate dose should be adjusted to maintain a urinary pH at 7 or greater. Serum samples should be assayed for creatinine levels and methotrexate levels at 24 hour intervals. If the 24 hour serum creatinine level has increased 50% over baseline or if the 24 hour methotrexate level is $>5 \times 10^{-6}$M or the 48 hour methotrexate level is 9×10^{-7}M or higher, the doses of calcium folinate should be increased to 100 mg/m^2 IV q 3 hours until the methotrexate level is $<10^{-8}$M. The infusion rate of calcium folinate should not exceed 16.0 mL (160 mg calcium folinate) per minute. Patients with significant third space accumulations should be considered high-risk and monitored until serum methotrexate levels are $<10^{-8}$M regardless of their 24 hour serum concentration.

The above mentioned statements on calcium folinate dosage do not apply with high-dosage methotrexate therapy. The dosages of calcium folinate have varied in different studies and the published literature on high-dosage methotrexate should be consulted.

In cases of massive overdose, hydration and urinary alkalinisation may be necessary to prevent the precipitation of the drug and/or its metabolites in the renal tubules. Neither standard haemodialysis nor peritoneal dialysis have been shown to significantly improve methotrexate elimination. Some clearance of methotrexate may be obtained by haemodialysis if the patient is totally anuric and no other therapeutic options are available. However, effective clearance of methotrexate has been reported with acute, intermittent haemodialysis using a high-flux dialysator.

Contact the Poisons Information Centre on 13 11 26 for advice on the management of an overdose.

PRESENTATION AND STORAGE CONDITIONS

Methoblastin (methotrexate) Tablets:

2.5 mg - yellow, round, biconvex, uncoated tablets engraved M 2.5 on one side and blank on the other, bottles of 30s

10 mg - yellow, capsule shaped, uncoated tablets engraved M 10 on the same side as the score line, bottles of 15s, 50s

NAME AND ADDRESS OF SPONSOR

Pfizer Australia Pty Ltd
ABN 50 008 422 348
38-42 Wharf Road
West Ryde NSW 2114
Australia

POISON SCHEDULE

S4 Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE ARTG

23 September 1991

DATE OF MOST RECENT AMENDMENT

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SPECIAL REPORT

Methotrexate Dosing Regimen for Plaque-type Psoriasis: A Systematic Review of the Use of Test-dose, Start-dose, Dosing Scheme, Dose Adjustments, Maximum Dose and Folic Acid Supplementation

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There is a range of methotrexate dosing regimens for psoriasis. This review summarizes the evidence for test-dose, start-dose, dosing scheme, dose adjustments, maximum dose and use of folic acid. A literature search for randomized controlled trials and guidelines was performed. Twenty-three randomized controlled trials (29 treatment groups) and 10 guidelines were included. Two treatment groups used a test-dose, 5 guidelines recommend it. The methotrexate start-dose in randomized controlled trials varied from 5 to 25 mg/week, most commonly being either 7.5 mg or 15 mg. Guidelines vary from 5 to 15 mg/week. Methotrexate was administered as a single dose or in a Weinstein schedule in 15 and 11 treatment groups, respectively; both recommended equally in guidelines. A fixed dose ($n=18$), predefined dose ($n=3$), or dose adjusted on clinical improvement ($n=8$) was used, the last also being recommended in guidelines. Ten treatment groups used folic acid; in 2 it was allowed, in 14 not mentioned, and in 3 no folic acid was used. Most guidelines recommend the use of folic acid. Authors' suggestions for methotrexate dosing are given. ***Key words: psoriasis; methotrexate; dosing; systematic review.***

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If topical medication and phototherapy are insufficient in controlling chronic plaque-type psoriasis (termed psoriasis in this article) the next step in the therapeutic strategy is systemic therapy, with methotrexate (MTX) frequently being used (1).

However, MTX has potentially serious side-effects, including myelosuppression, pulmonary fibrosis and gastro-intestinal disorders. The most prominent long-term side-effect is hepatotoxicity (2, 3). Folic acid (FA) is administered to prevent side-effects; however, this may reduce the efficacy of MTX (4, 5).

The US Food and Drug Administration (FDA) approved the use of MTX for the treatment of psoriasis in 1972 (6) before high-quality studies were accepted as the standard by which to judge efficacy and safety. Guidelines regarding the dosing regimen for MTX are partially based on expert opinions (2) and vary in their recommendations. In daily clinical practice there is a wide variety of dosing regimens (7) and patients with psoriasis are often undertreated (8). Barker et al. (9) have identified a number of key questions about MTX therapy for psoriasis and have emphasized the need for appropriate studies to determine optimal dosing with regard to efficacy and safety. A survey of dermatologists worldwide identified that the clinical use of MTX in psoriasis is not uniform and is not in full agreement with clinical guidelines (7).

The aim of this systematic review is to provide an up-to-date overview of randomized controlled trials (RCTs) using oral MTX monotherapy in adults for the treatment of psoriasis and to summarize evidence from these RCTs for the MTX dosing regimen regarding a test-dose, start-dose, dosing scheme, dose adjustments, maximum dose, and the use of FA. Also, recommendations from aggregated evidence (AgEv; guidelines and expert meetings) were summarized. Based on this review, initial suggestions for MTX dosing are given for future consensus and guidance in daily practice.

METHODS

Search strategy

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (10).

A search for RCTs and AgEv in the following databases was performed by an expert librarian (JL) from inception till 26 September 2013: MEDLINE (OVID), EMBASE (OVID) (both with a methodological filter to identify RCTs adapted from Cochrane (11)), the Cochrane Library complemented with a search of PubMed. TRIP and National Guideline Clearinghouse (NGC) were searched additionally for AgEv, complemented by AgEv known to the authors. The meta-register of controlled trials and clinicaltrials.gov were screened for ongoing trials. The search consisted of Subject Headings (if applicable), keywords and words in title and abstract for psoriasis and MTX. Reference Manager® software (version 12.0) was used to manage references.

Selection of articles

Two authors (SM and PD) independently selected all articles for eligibility, based on title, abstract and full-text. In cases of dis-

agreement, a third author (PhS) was consulted. RCTs had to fulfil the following inclusion criteria; reporting on efficacy; oral MTX monotherapy (topical therapy allowed); ≥ 10 adult patients treated with MTX (≥ 18 years of age); only including psoriasis patients (with ≥ 75% of patients having chronic plaque-type psoriasis).

AgEv was included if it contained clear recommendations regarding MTX dosing.

Risk of bias assessment RCTs

The risk of bias was assessed in duplicate by SM and PD independently using the Cochrane RoB tool (Table SI[1]).

Data extraction

Two authors performed data extraction independently (SM and PD). Study characteristics (author, country and year of publication, intervention, the number of patients in the MTX-treated group, duration of treatment and dosage regimen (including use of test-dose, start-dose, dosing scheme (daily, once weekly or in a Weinstein schedule (each weekly dose administered in 3 equally divided portions, given once a week, 12 h apart from each other)), dose adjustments, maximum dose and the use and dose/frequency of FA) and efficacy and safety data from MTX treatment groups were extracted from RCTs. The use of concomitant topical therapy was not further noted in this systematic review.

The number of patients who had a dose adjustment due to inefficacy (defined by individual study protocols) or side-effects was reported. For adverse event (AE) reporting, only the percentage of patients who had to stop MTX treatment due to (serious) side-effects was reported.

If outcomes were reported in a graph, data were extracted from these graphs.

From the AgEv, recommendations on MTX regimens were extracted.

Data reporting

For RCTs, study characteristics were summarized (Table I). Secondly, all efficacy outcome of RCTs making a head to head comparison of 2 or more MTX dosing regimens were reported (Table SII[1]). Thirdly, the most frequently reported outcome was identified to be used to compare results from RCTs comparing MTX with another active drug or placebo (Table SIII[1]).

In case of clinical homogeneity, a meta-analysis was performed according to the applicable methodology.

Data from AgEv are summarized in Table SIV[1].

In the discussion, evidence-based suggestions are made regarding MTX dosing regimen. Suggestions were primarily based on results from the RCTs, with AgEv used to support these.

RESULTS

RCT search result and study characteristics

The search identified 870 hits. A total of 847 hits did not meet the inclusion criteria. In total, 23 eligible studies with 29 treatment groups were included (Fig. S1[1]). The risk of bias of the included studies is reported in Table SII[1].

The included studies randomized 1,352 patients, of whom 1,206 were included in the final analysis. The loss to follow-up was mainly attributable to one study, in which 305 patients were randomized but only 202 patients were analysed (12).

Four studies compared 2 or more different MTX dosing regimens within a single study (12–15) (representing 10 treatment groups), 19 studies compared MTX with another active treatment (representing 19 treatment groups, 2 studies also used an additional placebo arm). The number of patients in each group ranged from 7 to 215. Summarized study characteristics are shown in Table I.

Efficacy outcome of included RCTs

RCTs making a head to head comparison between 2 or more MTX dosing regimens. Of the included RCTs, 4 compared 2 or more (fixed) different MTX dosing regimens within a single study (Table SIII[1]).

In 2002, Chladek et al. (14) found no significant difference between 7.5 mg $MTX^{Weinstein}$/week (n=12) and 15 mg $MTX^{Weinstein}$/week (n = 12). In 2005, Chladek (13) compared 4 different MTX dosing regimens and did not report whether there was a significant difference in

[1]http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-2081

Table I. *Summarized study characteristics of included randomized controlled trials (RCTs). In numbers of treatment groups*[a]

Test-dose	Start-dose	Dosing scheme	Dose adjustments	Folic acid
Yes: 2 (2.5–5 mg) (16, 48)	5 mg: 2 (16, 34)	Single: 15 (13, 15, 30, 31, 33–35, 42–46, 48)	Fixed dose: 18 (12–15, 30, 37, 39, 40, 42–45)	5 mg daily: 1 (48)
Not mentioned: 27	7.5 mg: 9 (13, 14, 17, 35, 38, 39, 41–43)	Two portions: 2 (37, 38)	Pre-defined dosing regimen: 3 (16, 41, 46)	5 mg daily except on MTX day: 4 (17, 30, 42, 46)
	10 mg: 4 (15, 37, 44, 48)	Weinstein: 11 (12–14, 16, 17, 32, 39–41)	Dose based on clinical improvement: 8 (17, 31–35, 38, 48)	1 mg/day except on MTX day: 1 (41)
	15 mg: 11 (12–14, 32, 33, 40, 45, 46) (1: 2.5 mg for 6 days/week (12))	Six portions: 1 (12)		5 mg the day before and after MTX day: 2 (15)
	25 mg: 1 (15)			5 mg the day after MTX day: 2 (34, 35)
	Weight-based: 2 (0.3 (30) and 0.5 (31) mg/kg/week)			Allowed: 2 (33, 38)
				Not used: 3 (12, 32)
				Not mentioned: 14

[a]Some studies contain more than 1 treatment group.
MTX: methotrexate.

efficacy between these 4 groups. Both studies included a relatively small number of patients.

Dogra et al (15) found no significant difference ($p > 0.05$) in patients achieving Psoriasis Area and Severity Index 75 (PASI75; meaning 75% improvement of PASI compared with baseline) with 10 mg/week MTX ($n = 30$, 25 analysed) vs. 25 mg/week MTX ($n = 30$, 26 analysed), though the time to reach PASI75 was significantly shorter in the 25 mg/week MTX group.

The fourth study, published by Radmanesh et al. in 2011 (12), found no significant difference in mean ΔPASI comparing 15 mg $MTX^{Weinstein}$/week (group 1, $n = 147$, 101 analysed) with 2.5 mg MTX 6 days per week (group 2, $n = 158$, 101 analysed) ($p = 0.0001$).

Outcome of RCTs comparing MTX with another active substance. To be able to compare results from RCTs comparing MTX with another active drug or placebo the most frequent reported outcome was identified. The PASI75 was identified as the most frequently reported outcome. In Table SIV[1] the results of different PASI75 obtained with different MTX dosing regimens are shown.

In 13 studies (with 15 MTX treatment groups) the percentage of patients attaining PASI75 ranged from 24% (16, 17) to 92% (15) at week 12 (results shown in Tables SIII and SIV[1]).

Meta-analyses

Because of clinical, methodological and statistical heterogeneity, illustrated by the many dosing regimens encountered (differences in start-dose, dosing scheme, dose adjustment, use of and dose of FA) and the diversity in outcome reporting (PASI in many ways and at different time-points), no data was pooled in a meta-analysis.

Aggregated evidence search results

The search included 9 guidelines (2, 18–25), 1 systematic review (3) and 1 consensus conference (6) (previous conferences leading to this conference were not included (26)). One guideline and one consensus conference were known to the authors and did not result from the search (27, 28). Three guidelines did not contain clear recommendations regarding MTX dosing for inclusion in this review (23–25).

Summary of aggregated evidence (AgEv) (Table SI[1])

Test-dose. Five out of 10 AgEv mention the use of a test-dose, and in 5 a test-dose is not mentioned. One recommends the use of a test-dose (29). One states that a test-dose can be considered, though there is no consensus in the guideline committee (27). Three recommend a test-dose in specific cases; for example, for elderly patients or patients with impaired kidney function (6, 19, 20). If a test-dose is recommended, the dose mentioned is 2.5–15 mg.

Start-dose. Eight out of 10 AgEv indicate what the start-dose should be, varying from 5 to 15 mg MTX (3, 6, 18, 20–22, 27, 28).

Dosing scheme. Two AgEv recommend administration in a single dose (18, 29), 5 state that a single dose or a Weinstein schedule can be considered (6, 19, 20, 27, 28) and 1 states a Weinstein schedule (21). Most state that there is no high-quality evidence for either (single or Weinstein schedule).

Dose adjustments and maximum dose. Almost all AgEv advise increasing or decreasing the dose based on efficacy. The maximum dose varies from 22.5 (21) to 30 mg (20, 27) MTX.

Folic acid. Seven out of 10 AgEv recommend the use of FA (3, 6, 18, 21, 27, 29), although its effect on reducing AEs remains unclear (22, 28). The FA dosing advised varies from 1 to 5 mg/day except on the day of MTX administration (2, 6, 21) to 5 mg the day after MTX administration (18).

DISCUSSION

This systematic review further highlights the wide heterogeneity in MTX dosing regimens in several aspects, such as the use of a test-dose, start-dose, dosing scheme, dose adjustment, maximum dose and FA. A great diversity in outcome reporting was found, thus it was not possible to pool the RCT data and no meta-analyses were performed.

Several aspects of MTX dosing regimens are discussed below and initial suggestions regarding the MTX dosing regimen for treating psoriasis are made based on the evidence available.

Test-dose

A test-dose was used in 2 out of 29 treatment groups and recommended (sometimes only in frail patients) in 5 out of 10 included manuscripts presenting aggregated evidence. A test-dose is administered to detect any unusual predisposition to toxic effects, such as myelosuppression, which usually occurs within 7–10 days (26). In AgEv a test-dose and laboratory control after one week is often suggested only for frail patients (for example elderly people or patients with impaired kidney function) (2, 6, 19, 20).

Start-dose

Amongst the included RCTs, start-dose varied from 5 to 25 mg/week MTX (Table I) and the best PASI75 response was obtained in a study using a start-dose of 25 mg/week MTX (15). Two studies based the start-dose on weight (30, 31). In the AgEv it is suggested to start MTX treatment with a dose ranging from 5 to 15 mg/week MTX (3, 18, 20–22, 27, 28). RCTs show that

starting with 15 mg/week MTX (32, 33) or increasing rapidly to 15 mg/week MTX (34) leads to a better PASI75 improvement compared with starting with 5 (16) or 7.5 mg/week MTX (35) and slow increases, or with a fixed dose of 7.5 mg/week MTX (17). The safety of the 15 mg/week MTX start-dose is illustrated by data from Barker et al. (33), where only 4% ($n = 8$) of patients stopped due to AEs (Table SIV[1]). In AgEv, it is suggested that start-dose may vary depending on severity of disease, age, kidney function and other co-morbidities (18, 21). MTX dose ≥ 15 mg/week MTX is suggested to have a more rapid onset of action compared with < 15 mg/week (36). The Psoriasis International Network survey has shown that 7.5 mg/week MTX is the most frequently used start-dose, and 15 mg/week MTX the second most frequently used start-dose (7).

Guideline recommendations on the subject of safety monitoring state that pre-treatment laboratory control is obligatory and advise laboratory control within one week after a test- or start-dose and every 2 weeks during the first 1–2 months. When at a stable dose of MTX or after 2–3 months of treatment, guidelines advise control every 2–3 months.

Dosing scheme

Four different methods of MTX dosing were encountered in the included RCTs (Table I). Daily low dosing (12) (high risk of bias, never suggested in AgEv), weekly dosing with each dose divided in 2 equal dosages (37, 38) (small studies with an intermediate/high risk of bias and never suggested in AgEv), dosing in a Weinstein schedule (12–14, 16, 32, 39–41), or a single weekly dose (13, 15, 17, 30, 31, 33, 34, 42–48), the last 2 most frequently used in clinical practice and suggested in AgEv (1). The Weinstein schedule is thought to decreases AEs (6, 20, 21), although this could not be concluded from included RCTs due to high risk of bias and small numbers of a study comparing single dose with Weinstein dosing (13). AgEv recommend the administration of MTX in a Weinstein schedule and in single dose, though there is little high-quality evidence supporting the use of one regimen over the other (6, 19–21, 27, 28).

Dose adjustments

A fixed dose was used in 18 treatment groups, in 3 a predefined dosing regimen was used and in 8 the dose was adjusted based on clinical improvement (Table I). It is generally accepted that MTX dose should be adjusted to clinical response, individualized per patient (6, 21, 28). Comparing 3 different studies (all low risk of bias, similar inclusion criteria) included in this systematic review (33–35), shows that starting with 15 mg/week MTX and adjusting the dose based on clinical efficacy at week 6 or rapidly increasing the dose to 15 mg/week MTX at week 2 with adjustment based on clinical efficacy at week 10 leads to a greater improvement and similar treatment termination due to AEs compared with slowly increasing the dose from 7.5 mg at week 0 to 15 mg at week 4 (Table SIV[1]). Due to the diversity in dose adjustments used in RCTs, no conclusion based on evidence from RCTs can be drawn regarding this topic. In AgEv, adjustment of the dose, based on efficacy or on AEs is advised. It has been suggested that, if an insufficient response is seen at week 8, the dose can be increased to 20 mg/week MTX (28). If with this dosing regimen, patients remain non-responders at weeks 12 (35) to 24 (34), the value of further dose escalation is unclear. Response to dose adjustments may take 4–8 weeks (6).

Maximum dose

The maximum dose of MTX allowed in one included RCT was 30 mg/week (48). In this RCT, it is unclear if 30 mg was actually administered. In another study, it was observed that increasing the dose from 20 to 25 mg/week provided little additional benefit; mean % change in PASI went from 16% to 25% in patients who had not previously obtained 50% improvement in PASI. The effect of increasing MTX to 25 mg/week in patients who have obtained 50% PASI improvement was not investigated (35). In AgEv maximum dose varied from 22.5 (21) to 30 mg/week (19, 20, 27).

Use of folic acid

The use of FA was mentioned explicitly in 10 treatment groups, in 2 it was allowed, in 14 it was not mentioned, and in 3 it was mentioned explicitly that no FA was used (Table I). Most aggregated evidence recommends the use of FA, although in a variety of dosing regimens. Comparing 2 studies with similar MTX dosing, where in the first no FA was used (32) and in the second 5 mg/week of FA was used (34), the use of FA seems to lead to less treatment termination. FA is thought to decrease the risk of AEs (49) and the (negative) influence on efficacy is debatable (5, 50). A meta-analysis performed in rheumatoid arthritis showed that administration of FA reduced the risk of gastro-intestinal side-effects, elevated liver enzymes or withdrawal from MTX for any reason. It did not appear to have a significant effect on efficacy, although only studies in which ≤7 mg/

Table II. *Authors' suggestions for methotrexate dosing regimen*

- Test dose: recommended for elderly or frail patients, for example patients with impaired kidney function.
- Start dose: 5–7.5 mg/week in elderly or frail patients and 15 mg/week in healthy patients.
- Administration as single dose. Use of the Weinstein schedule if gastro-intestinal complaints occur.
- Dose increase at week 8–20 mg/week if an insufficient response is seen.
- Maximum dose of 25 mg/week.
- Folic acid is recommended, though in what dosing and frequency remains unclear.

week FA was used were included in the analyses (51). The use of FA is recommended by an expert meeting to reduce the risk of hepatotoxicity, although there is no consensus on the optimal dosing regimen for FA (9).

Authors' suggestions

We have made suggestions below for several aspects of the MTX dosing regimen, based on this review (Table II).

Test-dose. We suggest a test-dose with laboratory control after one week only for frail patients (for example elderly people or patients with impaired kidney function). This suggestion is based on AgEv (Table SI[1]) and could not be based on RCTs.

Start-dose. Based on RCTs (33) we suggest a start-dose of 15 mg/week MTX with laboratory control after one week in healthy patients. It is known that the population included in RCTs is generally more healthy compared with the daily practise population. Therefore we suggest a start-dose of 5–7.5 mg/week MTX in frail patients (e.g. elderly people or patients with impaired kidney function) as suggested in AgEv (18, 21) (Table SI[1]).

Dosing scheme. Based on the fact that there is no high-quality evidence supporting increased efficacy or reduction in AEs by administration of MTX in a Weinstein schedule and administration in a single dose will probably increase drug compliance, we suggest administration of MTX in a single dose. If gastrointestinal complaints occur, a Weinstein schedule could be applied, though one should be aware that little high-quality evidence is available to support the schedule.

Dose adjustments. We suggest increasing the dose by 5 mg/week MTX at week 8 if an insufficient response is observed and no substantial AEs are observed. This is based on a recommendation from a consensus report (28). A further increase in the dose by 5 mg/week MTX is possible if 4–8 weeks after the dose increase the response is still insufficient. In good-responders dose reductions should be considered.

Maximum dose. We suggest a maximum dose of 25 mg/week MTX because the effect of a dose increase to 30 mg remains unclear and increase to 25 mg/week MTX has shown at least little benefit in patients who had not obtained 50% improvement in PASI (35). A maximum dose of 25 mg/week MTX is also most often recommended in AgEv (Table SI[1]).

Folic acid. We suggest the use of FA, though the dosing and frequency is debatable, varying from 1 to 5 mg/day (except on the day of MTX administration) to 5 or 10 mg/week, 24 or 48 h after MTX. This is based on data from RCTs (32, 34) and AgEv (Table SI[1]).

Strengths and weaknesses

By summarizing the dosing regimens and the efficacy obtained in RCTs of the treatment of psoriasis with oral MTX, and by systematically summarizing the MTX dosage regimens suggested in AgEv, this review creates evidence-based, initial suggestions regarding the MTX dosing regimen, which are more detailed than the existing recommendations in guidelines and consensus conferences. In a future consensus meeting or Delphi procedure, these data could form the basis for further recommendations attained amongst dermatologists worldwide. As mentioned before, more direct high-quality studies comparing the different aspects of MTX dosing regimens are needed.

There are many factors related to MTX dosing, but this review focussed on certain aspects. Due to the exclusion of patients under the age of 18 years and the exclusion of non-oral MTX administration no conclusions can be drawn regarding the treatment of children or the intramuscular/subcutaneous administration of MTX. Also, beyond the scope of this review are combination therapies with MTX (e.g. with etanercept (52)) and whether the optimal dose of MTX depends on factors such as body weight or kidney function. Results from RCTs are extrapolated for use in daily practise; however, it is known that the population included in RCTs is generally different from the population treated in daily practice. The RCT results included are relatively short term (maximum treatment time 52 weeks), but MTX side-effects, such as hepatotoxicity, often develop after years of treatment.

Conflicts of interest: SPM reports carrying out clinical trials for Abbvie, Amgen, Almirall, Novartis, and Pfizer. PMD, JL and LH report no conflicts of interest. PIS has had paid consultancies from LEO Pharma and AbbVie, and currently one from Novartis. She has one unrestricted grant from LEO Pharma. She is involved in the development of clinical trials that are independent of pharmaceutical company funding. She reports carrying out clinical trials for LEO Pharma, Janssen-Cilag, Almirall, Schering-Plough, Merck Serono, Amgen, Pfizer, Biogen Idec, Centocor, Roche, Eli Lilly, AbbVie, Celgene, Novartis and Astellas. She has no pharma- or industry educational grants. She has not personally received any educational grants from pharmaceutical companies to assist attendance at educational meetings.

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Clinical trial

Weekly vs. daily administration of oral methotrexate (MTX) for generalized plaque psoriasis: a randomized controlled clinical trial

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Abstract

Methotrexate (MTX) treatment for psoriasis is most often administered weekly, because the drug has been considered more hepatotoxic when taken daily. However, some patients may tolerate smaller, more frequent doses better.

Objective To study the efficacy and toxicity of daily vs. weekly MTX.

Patients and methods In a randomized controlled trial, 101 patients with generalized plaque psoriasis received oral MTX 2.5 mg daily for 6 days (Group 1), and another 101 patients received oral MTX 15 mg weekly (Group 2) in three divided doses (every 8 hours during a 24-hour period). Patients were followed monthly for 4 months as research participants, then for 1 year as part of their routine care. Complete blood counts, liver function tests, blood urea nitrogen, serum creatinine, urinalysis, and psoriasis area and severity index (PASI) scores were determined pre-treatment and at the following intervals after starting treatment: 2 weeks, 4 weeks and monthly for a total of 4 months. Changes in PASI scores were classified into three categories: >75% improvement was considered significant; 25–75% moderate; and <25% poor.

Results Sixty Group 1 patients and 81 Group 2 patients showed a significant response (*P*-value 0.001); 19 patients in Group 1 and 14 in Group 2 responded moderately; 22 patients in Group 1 and six patients from Group 2 responded poorly. Forty-five patients in Group 1 and 33 in Group 2 developed transient increases in liver enzymes (*P*-value 0.11). Nausea, headache, fatigue, and gastrointestinal upset were noted in four Group 1 patients and 30 Group 2 patients (*P*-value 0.0001).

Conclusion Nausea, vomiting, headache, and fatigue were significantly less common side effects in our patients who received MTX daily, but liver enzyme abnormalities were less common, and clinical efficacy was greater in the patients who received MTX weekly.

Introduction

Daily administration of methotrexate (MTX) is generally considered to be more hepatotoxic than weekly regimens. However, there are no controlled trials comparing the efficacy and side effects of daily vs. weekly MTX therapy for psoriasis or other dermatological disorders. Three basic dosage regimens are well described in the literature: weekly oral administration divided into three doses taken at 12-hour intervals;[1] single weekly oral dose;[2] and single weekly parenteral dose. We found that patients are more compliant with weekly divided doses taken at 8-hour intervals than at 12-hour intervals. We also found that if the total weekly dose is divided into six smaller doses and given daily for 6 days, patients experience less nausea, headache, and fatigue than when the drug is given in a single oral or parenteral dose or in divided weekly doses (at 8- or 12-hour intervals). Therefore, we attempted to compare the efficacy and side effects of daily vs. divided weekly oral MTX in patients with generalized plaque psoriasis.

Materials and methods

Three-hundred and five patients with chronic plaque psoriasis and no psoriatic arthropathy were randomly divided into two groups: 158 participants were scheduled to receive oral MTX 2.5 mg daily for six days (Group 1); and the second group of 147 participants was scheduled to receive oral MTX 15 mg weekly in three divided doses at 8-hour intervals (Group 2). No folic or folinic acid supplements and no topical or other systemic

medications were administered during MTX treatment. Strict contraception was recommended for the female patients of childbearing age. Fifty-three patients in Group 1 and 37 patients in Group 2 did not return regularly for follow-up and therefore were excluded. Another four patients from Group 1 and nine from Group 2 were excluded because of persistent liver enzyme elevations. No patient was diabetic. The remaining 101 Group 1 patients (34 females) and 101 Group 2 patients (51 females) were followed every two weeks for one month and then monthly for a total of four months as research participants and thereafter as routine outpatients for one year. The age range of the patients was 15–77 years (mean age was 37 years for Group 1 and 34 years for Group 2). Complete blood counts, liver function tests, renal function tests, and psoriasis area and severity index (PASI) scores were measured pretreatment, at two weeks and four weeks after start of MTX, and then each month for a total of four months. Clinical responses and improvement in PASI scores were recorded as improvement >75% significant; 25–75% moderate; and <25% poor.

Results

Sixty Group 1 patients and 81 Group 2 subjects showed a significant response (*P*-value 0.001). Nineteen from Group 1 and 14 from Group 2 responded moderately. Twenty-two patients in Group 1 and six in Group 2 responded poorly. Forty-five patients in Group 1 and 33 in Group 2 developed transient increases in liver enzymes (*P*-value 0.11, no significant difference). Nausea, fatigue, headache, and gastrointestinal upset were noted in four patients in Group 1 and 30 patients in Group 2 (*P*-value 0.0001, statistically significant; Tables 1 and 2).

The mean PASI scores for the patients in Group 1 were 11.9 at the beginning and 4 at the end of the study. The mean PASI scores for Group 2 were 15 at the beginning and 3.3 at the end of the study. The mean PASI score reductions for Groups 1 and 2 were not statistically significant at 7.9 and 11.7, respectively (*P*-value 0.13). Twenty-eight Group 1 female patients (54.9% of the female patients in this group) and 32 in Group 2 (94.1% of the female patients in this group) showed significant responses (*P*-value 0.001). Thirty-two Group 1 male patients and 49 Group 2 male patients showed significant responses (*P*-value 0.07, not statistically significant). No patient experienced serious side effects, such as irreversible liver damage, bone marrow suppression, or clinical respiratory symptoms during the research project or during the one-year follow-up.

Table 1 The response rate among patients of Groups 1 and 2

Response	Significant	Moderate	Poor
Group 1	60	19	22
Group 2	81	14	6

Table 2 Side-effects seen among Patients of Groups 1 and 2

	LER	NVF
Group 1	44	4
Group 2	33	30

LER, liver enzyme rising; NVF, nausea, vomiting and fatigue.

Discussion

MTX was introduced as a therapy for psoriasis in 1958,[3] and it remains one of the oldest and still one of the most effective treatments for all types of psoriasis. The main side effects of MTX are bone marrow suppression (with leukopenia, thrombocytopenia, and anemia), mucosal erosions including peptic ulceration, and irreversible liver cirrhosis. Lung toxicity is reported to be greater among patients with rheumatoid arthritis.[4] Bone marrow suppression and mucosal erosion are acute side effects, typically seen after administration of high doses. Liver enzyme elevation is also an acute side effect, which occurs more commonly with high doses. Hepatic fibrosis typically occurs after total cumulative MTX doses of at least 1.5 g.[5] The risk of hepatotoxicity may decrease if MTX is given in short courses and rapidly discontinued after clinical improvement.[6]

There are many patients with psoriasis for whom MTX is the best treatment choice but who cannot tolerate MTX because of side effects such as nausea, vomiting, and fatigue, which may occur with both parenteral and oral therapy. In our experience, nausea, vomiting, and fatigue develop significantly less often among patients treated daily rather than weekly. Based on peak serum concentrations of MTX reported to be at one hour parenterally and 1.6 hours orally,[7] and major excretion and metabolism within 24 hours,[8] we postulated that MTX may be more effective if given daily rather than weekly. However, in practice we paradoxically found a reverse result. Although significant clinical responses occurred more often in patients treated weekly, there were still many patients who responded well to daily MTX therapy, making the latter an option for those patients who do not tolerate the traditional weekly regimen. Long-term studies must be performed in order to verify the safety of such protocols. Regular laboratory monitoring is mandatory for all patients receiving MTX and should be stricter for those on a daily regimen.

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