Low dose methotrexate (5-25 mg/week) represents a major therapeutic advance in the management of RA in the last decade. Its established efficacy has led to it being used as the lead comparator drug in slow acting anti-rheumatic drug (SAARD) trials, to its increasing use in early disease, and to its inclusion in many drug combinations currently being evaluated. It seems to be the best tolerated SAARD with up to 75% remaining on it after 5 years [1]. Its therapeutic mode of action is still a matter of conjecture as low dose therapy is not anti-proliferative yet is still anti-inflammatory [2]. Its anti-inflammatory effect may be mediated by adenosine [3] although direct effects on cytokine and eicosanoid production have been claimed.

Methotrexate's pharmacodynamics vary, absorption and excretion differing enormously and unpredictably between individuals as well as being influenced by measurable factors such as renal function and concomitant therapies including NSAIDs and probenicid. The latter can elevate methotrexate levels by 400% [4]. This is important when assessing the relative efficacy and side effects in individual patients.

Minor adverse reactions with methotrexate are relatively common but generally do not result in treatment discontinuation. This contrasts with other SAARDs e.g. myocrisin, minor reactions to which often lead to stopping therapy when temporary cessation or dosage reduction, may be more appropriate [5]. Non life-threatening methotrexate side effects such as nausea or diarrhoea may be improved by dosage adjustment, altering route of administration from oral to parenteral or using divided weekly dosage. Increased nodulosis is an unusual but well-recognized occurrence with methotrexate [6]. Other less serious but troublesome adverse reactions such as minor stomatitis, alopecia and skin rashes are self-evident and can be treated according to their severity by withdrawal of therapy, dosage adjustment or topical treatment. It has been suggested that methotrexate is associated with increased post-operative infections or delayed wound healing and that it should be stopped pre-operatively. Several small prospective studies have not confirmed such an effect [7, 8], yet a definitive answer requires a much larger study.

The more potentially lethal adverse haematological, pulmonary and hepatic reactions seem to be associated with an older group, renal impairment and relative folate deficiency. There is some evidence that folate supplements cause no loss of efficacy and protect against toxicity [9]. Serious haematological toxicity seems to be relatively rare [10] and is usually treatable by folic acid rescue. The relationship of serious haematological toxicity to co-administration with trimethoprim/sulphamethazole is established yet its combination with another folate antagonist, sulphasalazine, has not shown the same problem [11]. One difficult problem facing the clinician is the patient on low dose methotrexate who develops dyspnoea. This may represent infection by a common respiratory pathogen, opportunistic infection (e.g. with *Pneumocystis carinii*), methotrexate pneumonitis, or an unrelated problem. Methotrexate pneumonitis is a potentially life-threatening complication, probably a hypersensitivity phenomenon, which is reversible on stopping treatment and giving steroids [12]. The pneumonitis appears to not to be dose related. It is recommended that all patients have a pre-treatment chest X-ray (and possibly pulmonary function tests) to check for pre-existing lung disease. Another theoretical side effect of methotrexate is oncogenicity, but there is no clear evidence to indicate this as a problem [13].

The clinician perhaps worries most about whether he is accumulating a cohort of rheumatoid patients who are developing irreversible liver damage. In last month's issue of the *Journal* [14], three cases of cirrhosis are described in elderly male RA patients treated with methotrexate. All three patients had received over 3 g of methotrexate and their findings suggest an incidence of significant liver disease of 9.4/1000 at 5 yr as opposed to Walker et al. [15] who estimated an incidence of 1/1000 at 5 yr. The American College of Physicians recommended liver biopsy after 2-3 yr of methotrexate treatment which has been regarded by some as excessive [16, 17]. In some studies treatment discontinuation has been instituted if there was a sustained elevation of transaminases above three times the upper limit of normal [18]. Guidelines have recently been issued by the ACR based on expert analysis of published experience with methotrexate [19]. Prior to starting treatment alcohol consumption should be reviewed and restrictions on alcohol consumption stressed to the patient; baseline liver function tests, hepatitis B and C serological studies should be checked; pre-treatment liver biopsy should be considered in the presence of persistently raised transaminases, positive hepatitis serology or a history of alcohol abuse; liver function tests should be checked every 4-8 weeks throughout treatment. If transaminase levels are elevated in more than six of the 12-monthly (or five of nine if tests are 6-weekly) monitoring tests performed, liver biopsy or treatment discontinuation should be considered. While recognizing the differences in clinical practice between Europe and North America, there is a compelling argument that guidelines like these be considered mandatory because of the future potential medicolegal and resource implications.

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Intravenous immunoglobulin therapy (IVIg) has emerged over the last decade since the seminal reports of Imbach [1] and Fehr [2] as a potentially useful immunomodulator in a number of rheumatological diseases. These include systemic vasculitis, SLE, refractory RA, systemic juvenile chronic arthritis (JCA), polymyositis, anticardiolipin antibody (ACA) associated recurrent miscarriage syndrome and Kawasaki's disease. At present the proven indications for IVIg are primary antibody deficiency, immune thrombocytopenic purpura (ITP) and Kawasaki's disease. There are relative indications for its use in the secondary immunodeficiency of AIDS and haematological malignancies. We review its rheumatological uses, proposed mechanisms of action and adverse reactions.

Injected gammaglobulins were first used in the 1950s to treat hypogammaglobulinaemia and in 1981 IVIg became available for clinical use [3]. IVIg is fractionated from normal plasma and contains over 90% IgG with trace quantities of IgA (depending on the preparation) which is screened for hepatitis B, C, HIV I and II and elevated amidotransferase. Each batch of IVIg is prepared from a pool of 10 000–20 000 healthy blood donors. IVIg thus contains a broad spectrum of the expressed normal human IgG repertoire of antibodies.

No case of documented transmission of HIV or viral hepatitis has been reported with the new formulations which have additional viral inactivation processes like acid treatment and pasteurization.

An early report on the benefit of human placenta-eluted gammaglobulin [4] stimulated small clinical studies on the use of IVIg in RA [5–7]. These studies report initial improvement in clinical and biochemical parameters which do not persist when the treatment is stopped. Tumiati [7] reported that nine out of 10 patients who had failed on at least one DMARD had subjectively and objectively improved within 4 weeks of commencing IVIg and this improvement was maintained by monthly boluses for 6 months. After discontinuation of therapy all patients had a relapse of their disease within 12 weeks, suggesting the effect achieved was not disease remittive.

Emery and colleagues have reported on the first placebo-controlled study of IVIg in 32 patients with early RA who had not received second line agents [8]. The actively treated group had two consecutive days treatment at a dose of 0.5 g/kg/day followed by a single monthly treatment. While there was a significant fall in RF titre and an increase in immune complexes in the actively treated group there was no significant differ-