EDITORIALS

METHOTREXATE IN RHEUMATOID ARTHRITIS: TOXICITY ISSUES

It has been 10 yr since the initial randomized placebo-controlled trials were published which established the short-term efficacy of low-dose weekly methotrexate in rheumatoid arthritis [1, 2]. For the past 10 yr there has been an extensive clinical research programme including comparative studies of methotrexate versus auranofin [3], azathioprine [4], i.m. gold [5] and cyclosporin A [6], and long-term prospective studies [7-9]. There is now little debate about the efficacy of methotrexate in rheumatoid arthritis. Methotrexate is now the most popular second-line therapy utilized in the USA for the treatment of rheumatoid arthritis. The enthusiasm and interest in this compound have expanded, and include our colleagues worldwide.

It is timely to re-emphasize the toxicity profile of methotrexate. Toxicity is the major reason for methotrexate discontinuation [9, 10]. The most common side-effects of low-dose methotrexate are gastrointestinal toxicities, including anorexia, nausea, stomatitis and diarrhoea. Central nervous system toxicity, including headaches, dizziness, fatigue and mood alterations, may also occur. Many of these side-effects can be reduced by supplemental folate acid, 1 mg/day. Folic acid at this dose decreases many side-effects without interfering with the efficacy of the drug [11, 12]. When folic acid is not successful in improving side-effects, a trial of folic acid administered 8-12 h after methotrexate may be effective [13].

Haematological toxicity with methotrexate is uncommon. Leucopenia, thrombocytopenia, megaloblastic anaemia and pancytopenia may occur. In almost all cases of haematological toxicity, an identifiable risk factor can be found. These risk factors include untreated folate deficiency, renal insufficiency, the use of methotrexate during a superimposed infection and the concomitant use of selected drugs such as trimethoprim/sulphamethoxazole or probenecid.

Methotrexate is teratogenic; women of child-bearing potential should not become pregnant while taking it. Several decades ago, methotrexate was used as an abortifacient and it has again been proposed as such an agent [14]. Women of child-bearing potential must discontinue methotrexate for at least one menstrual cycle prior to attempting conception.

Until recently, no carcinogenic effect of low-dose methotrexate had been demonstrated in either patients with psoriasis or rheumatoid arthritis. Recently, non-Hodgkin's (B-cell) lymphoma which reversed with methotrexate discontinuation has been reported in patients with rheumatoid arthritis [15-17]. Epstein-Barr virus was expressed in the tumour cells. The regression of the tumour without chemotherapy is a rare event in the course of non-Hodgkin's lymphoma. This suggests a relationship between this lymphoma and the drug. This spontaneous resolution of the lymphoma with drug discontinuation has been observed with other immunosuppressive therapies, including azathioprine and cyclosporin A when used in organ transplantation.

Opportunistic infections are rare with methotrexate, but include localized and disseminated zoster, fungal infections and Pneumocystis carinii infection.

Pulmonary toxicity remains a concern. This month's issue of the British Journal of Rheumatology contains two papers on the lung and methotrexate. One is from France describing the experience at Cochin Hospital with pulmonary complications in rheumatoid arthritis patients receiving methotrexate [18]. Their experience is similar to that previously observed. In the second paper, investigators from Switzerland prospectively studied pulmonary function in rheumatoid patients treated with methotrexate [19]. They reported that there was no significant change in pulmonary function in patients receiving low-dose weekly methotrexate for rheumatoid arthritis. Routine pulmonary testing did not identify patients who subsequently developed pulmonary disease. In fact, this study confirms that routine pulmonary function testing is not indicated in patients receiving low-dose methotrexate for rheumatoid arthritis. Identification of risk factors for the development of methotrexate pneumonitis has been an area of intense study. Several small studies suggested a relationship between pre-existing lung disease and the development of methotrexate pneumonitis [20-22]. At last year's American College of Rheumatology meeting, investigators reported a multicentre case-control study in which risk factors for methotrexate lung disease were identified, and included age, diabetes and the presence of pleuropulmonary disease prior to methotrexate administration [23]. As with other studies, disease duration, methotrexate duration, and weekly and cumulative doses were not risk factors for this side-effect. Whether rheumatoid arthritis patients are at greater risk for developing this side-effect as compared to patients receiving methotrexate for other diseases is unknown.

There is little debate that methotrexate is hepatotoxic. Risk factors associated with liver toxicity in psoriatic patients receiving methotrexate include insulin-dependent diabetes, morbid obesity, renal insufficiency, alcohol consumption, daily or several methotrexate doses per week and cumulative dose of methotrexate [24]. Based on the association of hepatotoxicity with cumulative dose, the dermatology community has recommended routine liver biopsies.
based on total dose [24]. The experience in rheumatoid arthritis patients fortunately has not paralleled that seen in psoriasis. The risk of serious liver disease, defined as either cirrhosis or clinically decompensated liver disease, has been projected to be less than 1 out of 1000 cases after 5 yr of treatment among patients with active rheumatoid arthritis [25]. In this case-control study, all of the patients who developed serious liver disease developed liver blood test abnormalities which included either elevations in serum transaminases or a low serum albumin. This study and the large published clinical experience with the drug led to the development of guidelines for monitoring patients with rheumatoid arthritis receiving methotrexate. A committee of the American College of Rheumatology assessed the risk for the development of clinically significant liver disease during methotrexate treatment, evaluated the risk and role of surveillance liver biopsies, and provided recommendations for monitoring patients for liver toxicity [26]. These guidelines recommended baseline liver blood tests and hepatitis B and C serology prior to starting treatment with methotrexate. The importance of monitoring serum transaminases and albumin every 4—8 weeks while on methotrexate therapy was emphasized. Routine surveillance liver biopsies were not recommended for rheumatoid arthritis patients receiving traditional doses of methotrexate (< 20 mg/week) in the setting of normal liver blood tests. However, biopsies were recommended for patients who developed persistent abnormalities in liver blood tests.

A recent paper studied the effectiveness of the guidelines in predicting liver disease in 112 patients with rheumatoid arthritis [27]. These patients underwent liver biopsies according to the guidelines of the Psoriasis Task Force [24]. The guidelines of the American College of Rheumatology [26] were then retrospectively applied to test their usefulness and cost effectiveness in this population. The ACR guidelines were felt to be clinically useful and resulted in considerable cost savings. There was, however, one patient, an insulin-dependent diabetic, who developed cirrhosis despite consistently normal liver blood tests. This patient would not have been identified using the ACR guidelines, which included either elevations in serum transaminases or a low serum albumin. This study and the guidelines recommended baseline liver blood tests and hepatitis B and C serology prior to starting treatment with methotrexate. The importance of monitoring serum transaminases and albumin every 4—8 weeks while on methotrexate therapy was emphasized. Routine surveillance liver biopsies were not recommended for rheumatoid arthritis patients receiving traditional doses of methotrexate (< 20 mg/week) in the setting of normal liver blood tests. However, biopsies were recommended for patients who developed persistent abnormalities in liver blood tests.

It is gratifying to observe the worldwide interest in methotrexate. There are still many unanswered questions about this exciting compound. Further clinical and basic research with the drug is encouraged.

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REFERENCES


PAIN is one of the major symptoms of inflammation, and it is the one that affects patients most. In healthy joints, pain is only evoked by high-intensity stimuli, such as twisting of the joint or strong pressure. By contrast, in inflamed joints, pain may be present in the absence of intentional stimulation (resting pain), or it may be elicited by normally non-painful mechanical stimuli such as movements in the working range of the joint or gentle pressure applied to the joint. Research into the mechanisms of nociception under inflammatory conditions attempts to gain insights into the neuronal events involved.

In general, the neurobiological response to noxious or painful stimuli is more complex than previously thought. Recent research has revealed that under clinically relevant conditions such as inflammation, the nervous system does not simply react to noxious stimuli; it undergoes changes that modify the neuronal processing of nociceptive stimuli (functional neuroplasticity) [1-4]. In a state of inflammation-evoked neuropasticity, sensory stimuli such as the application of pressure to a joint may evoke much larger responses in the nervous system than under normal conditions. Functional neuroplasticity is thought to be of major importance for the generation of clinically relevant pain [1-4].

The sensitization (increase in excitability) of afferent nociceptive fibres (nociceptors or 'pain fibres') to mechanical, thermal and chemical stimuli is a major component of the generation of inflammatory pain. Articular nociceptors in a healthy joint respond only to noxious (painful) stimuli such as twisting of the joint or intense pressure applied to the joint. During inflammation, nociceptors are sensitized. Then they are activated by normally non-painful stimuli such as light pressure onto the joint or movements in the working range of the joint. Hence, the message 'noxious stimulus' is signalled to the spinal cord by innocuous stimuli which are usually not painful. Another group of articular nociceptors does not even respond to noxious mechanical stimulation of the normal joint. A high proportion of these initially mechanoinensitive (silent) nociceptors are also sensitized during inflammation and start to respond to mechanical stimuli. The sensitization of joint nociceptors is induced by inflammatory mediators such as prostaglandins, bradykinin and others (for details, see [4]).

Recently, the functional neuroplasticity in the spinal cord has been a major focus of research [1-4]. Spinal cord neurons can be sensitized as well. During an experimental inflammation in the knee joint, spinal cord neurons with input from the knee exhibit an increased sensitivity towards the afferent inputs from the inflamed joint [4, 5]. This can be expected from the increased afferent input in sensitized nociceptors [4]. However, these neurons also exhibit enhanced responses to afferent inputs from non-injured regions of the leg which are adjacent to or even remote from the inflamed site [4, 5]. This suggests that the spinal cord neurons are not just excited by the enlarged afferent input from the inflamed joint, but that they are rendered hyperexcitable. This 'central sensitization' leads to an amplification of the spinal nociceptive processing [1-5].

The cellular mechanisms involved in the generation and maintenance of spinal cord hyperexcitability are currently being investigated. The development of hyperexcitability is dependent on the release of...