characterized by low CK levels during flares in the face of obvious histological changes, and therefore this was not adequate to demonstrate response. Given her prolonged course and poor muscle mass at this stage, we expected subtle clinical changes with minimal initial improvement in muscle strength.

Infusions (5 mg/kg) were administered at weeks 0, 2, 6 and 14. She continued with prednisone and mycophenolate. A remarkable response was observed in muscle strength after only two infusions. She could now walk and was able to lift her arms above her head. The CMAS scores demonstrated a response (Fig. 1). Function and endurance was still impaired but improving.

After the third infusion, she presented with a perforated peptic ulcer requiring laparotomy and oversew of the ulcer. She was hospitalized for 2 weeks post-operatively. This raised the interesting point of the relationship between anti-TNF treatment and aggravation of underlying peptic ulcer disease. With increasing use of anti-TNF therapy, it would be interesting to see if this is reported elsewhere. Although this raised an interesting question, we felt that anti-TNF therapy was unlikely to be the culprit as she had a long-standing history of peptic ulcer disease and prednisone use.

She received the fourth infusion as planned but had a decline in muscle function prior to this (Fig. 1). This raised a number of issues. The recent major surgery and prolonged hospitalization with resultant deconditioning could have contributed to the decline in response. Secondly, we had used the dosing frequency recommended in rheumatoid arthritis. The optimal dosing frequency (e.g. 4-weekly vs 8-weekly) and dose strength (e.g. 5 mg/kg vs 10 mg/kg) [4] has not been determined, and may be different in PM. We increased the infliximab dosing frequency to 4-weekly intervals to assess the role of dosing frequency. This resulted in continued gains in muscle strength with infusions 5 and 6 (Fig. 1). Our patient tolerated the drug well and has experienced no adverse events thus far.

The experience with anti-TNF therapy in PM and DM remains limited, with variable response to anti-TNF therapy (both infliximab and etanercept) having been described in case reports thus far [4–9]. In our case, we were encouraged by the initial response in our patient with long-standing debilitating PM who had tried and failed conventional and experimental DMARDs necessitating prolonged steroid use. Clearly, controlled studies are needed to clarify the important issues of response, appropriate dose and dosing intervals with the use of anti-TNF therapy in refractory PM and DM.

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Folic acid supplementation during methotrexate treatment: nonsense?

Sir, We read with interest Whittle and Hughes’s review concerning methotrexate (MTX) and supplementation with folate in the treatment of rheumatoid arthritis (RA), in which concomitant folate administration is demonstrated to be useful to reduce MTX adverse effects, as proven in numerous trials [1]. Nevertheless, there are conflicting opinions on the real benefits of folate supplementation and no guidelines exist regarding doses and timing of its use [1]. In our opinion, low doses of MTX, without concomitant folate administration, are well tolerated for long periods in the absence of adverse events. Folate supplementation should be administered only in circumstances leading to folate deficiency in order to prevent MTX adverse effects. On the basis of our experience, gastroduodenal atrophy should be included among these.

The following describes a patient with RA, benefiting from treatment for 4 yr with MTX (10 mg/week without folate). In September 2003, following disease reappearance, the dose was successfully increased to 12.5 mg/week. Laboratory parameters were normal, including white cells, haemoglobin (Hb) and Mean Corpuscular Volume (MCV).

In January 2004, the patient developed bronchopneumonia with cough, stomatitis, fever, asthenia, anorexia and diarrhoea, and was treated with ceftriaxone for 1 week. Resolution of respiratory involvement followed, but gastrointestinal symptoms persisted.
In April 2004, after self-decided MTX suspension, the patient presented with severe asthenia. Blood examinations showed macrocytic anaemia (Hb 10.0 g/dl, MCV 109.4 fl). Testing for faecal occult bleeding proved negative. An endoscopy and histological analysis on biopsy specimens showed chronic atrophic gastritis and severe duodenal villous atrophy. Tests for Helicobacter pylori (H. p) proved negative. Coeliac disease and autoimmune gastritis were excluded by the absence of specific antibodies, and IgA serum levels were normal. Folate deficiency was present (folate level <3 ng/ml), with a normal vitamin B12 level. Treatment with folic acid (5 mg/day) was started, leading to complete resolution of symptoms and laboratory data in 3 months. A later endoscopy with biopsy showed the resolution of gastrointestinal involvement.

The use of MTX to treat RA has been well documented since 1951 [2]. Since no guidelines exist, folate supplementation has been associated with MTX to reduce toxic effects. Indeed, many well-known adverse effects, such as enteropathy, gastrointestinal intolerance, stomatitis, alopecia and cytopenia, have been explained by the antifolate properties of the drug [3]. Many randomized clinical studies demonstrate that folate administration may reduce side-effects with no relevant influence on MTX efficacy [1–4].

Nevertheless, in other trials, prophylactic use of folate has been shown to require a higher dose of MTX to achieve the same therapeutic response compared with folate supplementation [5]. Furthermore, van Ede et al. showed that folate supplementation can significantly reduce the incidence of high liver enzyme levels, but seems to have no effect in preventing other adverse events, including gastrointestinal and mucosal side-effects [6].

According to our latest observations, our case confirmed that low doses of MTX without folate supplementation could be administered over long periods without adverse reactions, as reviewed by Endresen and Husby [7]. In a recent study [8], Hoekstra et al. demonstrated that MTX side-effects occur most commonly in patients with high body mass index or prior gastrointestinal events, and in females. Nevertheless, toxicity of MTX is exacerbated by folate deficiency, which could result from differing dietary habits, or may be induced by events such as infectious disease or/and antibiotic therapy. It has been shown that folate availability is inversely correlated with the severity of clinical status and is lower in septic feverish patients [9]. These conditions could increase folate demand due to a competitive mechanism in daily absorption [10]. Penicillin administration leads to a block of folate synthesis of the intestinal bacteria, which also occurs during diarrhoea or inflammatory bowel diseases. MTX treatment may increase folate requirement because of competitive metabolism in its utilization, producing a state of folate deficiency.

Since MTX in RA treatment is likely to act by inhibiting the replication of cells with high turnover (although the anti-inflammatory effects of MTX are mediated by adenosine release), it may reduce replication of immune, inflammatory and epithelial cells. Therefore, alongside the effects of MTX treatment, enteric involvement is already known, including all symptoms and complaints of the mouth and the upper or lower abdominal tract. Our case demonstrated that, among gastrointestinal side-effects, we should also include gastroduodenal atrophy, never previously described in the literature.

In our opinion, although folate use reduces the rate of side-effects of MTX treatment, the guidelines for folate supplementation should state that folate should be added only when its actual demand increases, such as during an infectious disease or during antibiotic therapy, as in our patient. Supplementation should not be given routinely because a normal diet can ensure an adequate amount of this vitamin and it can impair MTX therapeutic effects. Prophylactic folate for all RA patients on MTX is not strictly required, except in the case of increased folate requirement.

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