Comment on letter by Deray

Sir,

In his letter, Deray has attempted to identify a single, fixed dose conversion ratio when switching patients from epoetin to darbepoetin alfa therapy and has concluded that this ratio is not the same for the intravenous (i.v.) and subcutaneous (s.c.) routes of administration [1].

In trying to identify single, fixed dose conversion ratios by the s.c. and i.v. routes, Deray has compared the results from a European study in epoetin-naïve pre-dialysis patients [2] with a US study in haemodialysis patients receiving prior stable epoetin therapy [3]. As neither of these studies was designed to investigate conversion methodologies and as they involve different patient populations and routes of administration, it is misleading to draw conclusions from them about conversion ratios.

Furthermore, as has been pointed out previously [4,5], the implementation of a single, fixed dose ratio to convert patients from epoetin to darbepoetin alfa is not appropriate for either the i.v. or s.c. routes of administration, as the relationship between epoetin and darbepoetin alfa doses is non-linear. As well as being influenced by prior epoetin dose, the conversion ratio will also be influenced by other factors such as dosing interval. This is why the European prescribing information for darbepoetin alfa suggests 200:1 as an initial conversion ratio (based on equivalent peptide mass) but notes that ‘titration to optimal therapeutic doses is expected for individual patients’. In the two studies cited by Deray, 42 [2] and 69% [3] of patients required further dose titration after starting darbepoetin alfa. In the first study, the patients had been naïve to all epoetin-related therapies, prior to starting darbepoetin alfa. In the second study, patients were switched from epoetin to darbepoetin alfa therapy.

It is therefore incorrect to speculate, on the basis of single conversion ratios calculated from mean data from dissimilar studies, that switching from SC epoetin to darbepoetin alfa would necessitate a dose increase of 20–30%. As I stated in my original article [6], formal head-to-head studies are required before any definite conclusions can be made about the relative cost–benefit of these two therapies.

Lastly, Deray cites an abstract by Hörl [7] to support his contention that switching from darbepoetin alfa once every 2 weeks to a 3-week dosing schedule necessitates a 13% increase in dose. However, this abstract does not make any mention about 3-week dosing, so it is difficult to understand how he reached this conclusion. Studies in dialysis patients have shown that there is no dose penalty associated with changing from darbepoetin alfa dosing once every 2 weeks to once every 3 weeks [8] and, likewise, only a 0–2.2% increase in total weekly dose was necessary when changing to dosing once every 4 weeks [8,9]. Again, more controlled studies are required to examine the true cost-effectiveness of darbepoetin alfa dosing less frequently than once per week.

I completely agree with Deray in that attempts to reduce the total cost of anaemia therapy are of the utmost importance to allow more patients to benefit. Pending further studies, and for this reason, treatment should be individualized to each patient’s particular requirements, rather than by indiscriminately applying arbitrary dosing algorithms.

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Myalgia: an uncommon or underestimated side effect of mycophenolate mophetil after transplantation?

Sir,

Mycophenolate mophetil (MMF) is widely used after transplantation and in several autoimmune disorders.
Because of its recent introduction and its use in combination with other drugs, uncommon or overlapping side effects, such as severe myalgia, may be difficult to detect.

According to a systematic search on Medline and Embase (to 2003, week 38; combining Mesh-Emtree and free terms related to MMF and to muscle-myalgia), only four of the 317 titles retrieved described myalgia as a severe or common MMF side effect. These four papers dealt with autoimmune diseases (uveitis, psoriasis and Wegener granulomatosis) [1–4]; a further report suggested a facilitating effect on myalgia during quinupristin-dalfopristin therapy [5].

Even if myalgia is considered among the side effects of MMF in clinical trials, its severity is usually minor and it is not considered among the common causes of drop-out from MMF [6].

We would like to bring attention to this uncommon side effect, by reporting on two patients who developed severe, invalidating myalgia, presumably linked to MMF, after kidney and pancreas grafts.

Case 1. A 42-year-old type 1 diabetic woman underwent a successful pancreas graft, in the presence of laser-treated retinopathy, neuropathy, and biopsy-proven diabetic nephropathy. Chronic immunosuppressive therapy consisted of tacrolimus (levels 10–15 ng/ml in the first 2 months, 8–12 ng/ml at 3–12 months), MMF 2 g, methylprednisone tapered at 5 mg/day at 6 months.

Before transplantation, during a tacrolimus-challenge test to assess her renal reponse, her tacrolimus levels reached 42 ng/ml, and remained above 20 ng/ml for a week (presumably because of the interaction with bioflavones contained in herbal teas). During this episode, she experienced all main tacrolimus side effects, including nausea, vomiting, anxiety, insomnia, restless leg syndrome and lower limb neuropathy. The symptoms progressively disappeared with tacrolimus clearance.

Since the early post-transplant period, she complained of muscular pain, particularly in the lower limbs, which was exacerbated by exercise, but present also at rest. The symptoms were reported as completely different from those experienced during tacrolimus challenge. Three months after transplantation, the myalgia was severe enough to impair her daily activities.

Renal function was in the normal range (serum creatinine 0.8 mg/dl, creatinine clearance 96 ml/min, physiological proteinuria). Tacrolimus levels were in the prescribed range; support therapy consisted in trimethoprim-sulphametoxazole, acetylsalicylate and omeprazole.

Viral, immunological and metabolic-endocrinologic tests were normal; therefore, the myalgia was hypothesized as pharmacological, but unrelated to tacrolimus, and unresponsive to corticosteroid tapering. Consequently, an adverse effect of MMF seemed the most likely explanation. MMF kinetic was tested (2 months after graft: basal level 1.8 μg/ml, second hour 9 μg/ml; 5 months after graft: basal level 2.2 μg/ml, second hour 11.3 μg/ml); even though the ‘ideal levels’ were not yet fully defined in the literature, MMF was reduced from 2 to 1.5 g/day; the symptoms improved in few days and disappeared in 3 weeks.

Case 2. A 57-year-old man, a recipient of a renal graft 12 years before (serum creatinine 1.2 mg/dl, creatinine clearance 102 ml/min, microalbuminuria, normal blood count and liver tests), was switched from azathioprine to MMF because of severe gouty arthritis, to allow allopurinol therapy. Further therapy (cyclosporin A 200 mg/day, acetylsalicylate and isosorbide mononitrate) was unchanged. A few days after starting MMF (1 g/day), he complained of diffuse arthromyalgic aches, mainly in the lower limbs, fatigue and ankle oedema. The myalgia was severe enough to require a return to azathioprine, 2 weeks later. Rapid improvement was observed, with complete recovery within 1 week.

During the short period of MMF therapy, cyclosporin A levels were in the prescribed range (basal prescribed range 80–120 ng/ml; levels 84, 121 ng/ml), and support therapy was unchanged.

Interestingly, in both cases, the usual adverse effects of MMF were not recorded: gastrointestinal symptoms and leucopenia were both absent, and serum immunoglobulins were in the normal range in case 1, in which they were periodically tested. Case 1, however, was severely anaemic (haemoglobin nadir 7 g/dl, with slow response to darbepoetin alpha). Even if less common than isolated leucopenia, anaemia is also reported as side effect of immunosuppressive regimens containing MMF, in particular in the first phases after transplantation.

As it occurs in the case of relatively new drugs, the pharmacological interactions are only partially known and a role of concomitant therapies cannot be excluded. However, the two patients did not share any immunosuppressive agent, nor any support therapy, with the exception of acetylsalicylate at low doses, and the calcineurin inhibitors (tacrolimus in case 1 and cyclosporin A in case 2), known to interfere with MMF metabolism, were in the usual ranges in both, thus suggesting an individual predisposition in the development of this unusual problem.

Even if only an MMF challenge could definitely prove the role of the drug, the myalgia was severe enough to avoid proposing such a trial to these two patients.

Solid organ transplants are the most common worldwide indication for MMF. The concomitant use of corticosteroids, known to induce myopathy, and of calcineurin inhibitors, whose side effects include neuropathic pain, may mask the presence of this occasionally severe MMF side effect.

Higher awareness may lead to its precise quantification in transplantation medicine.

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