Mycophenolate mofetil for the treatment of autoimmune diseases: hype or hope?

Like other drugs before it, mycophenolate mofetil (MMF) was introduced into the treatment of "autoimmune diseases" after successful use in transplantation medicine for prevention or treatment of graft rejection. Since physicians caring for patients with autoimmune diseases are increasingly using MMF, it is time to question the rationale behind its use.

By inhibition of purine nucleotide synthesis MMF appears to act preferentially on activated lymphocytes, which are thought to play a major role in autoimmune processes. Mycophenolic acid, the active metabolite of MMF, selectively inhibits inosine 5'-monophosphate dehydrogenase, a key enzyme of the purine de novo synthesis pathway of guanosine nucleotides [1]. There are two pathways for guanosine production, the de novo pathway and the salvage pathway. In activated lymphocytes the de novo pathway is dominant. Blocking the de novo pathway through mycophenolic acid is thought to be responsible for the reduced proliferation of T lymphocytes in vitro, and possibly explains immunosuppressive effects of MMF in vivo.

MMF has indeed proven effective in suppressing immune reactions, more specifically alloimmune reactions in patients after solid organ transplantation [2]. This suggests the strong probability of an inhibitory effect of MMF not only on alloimmune reactions but also on autoimmune reactions, because T lymphocytes are potentially involved in both. These and other considerations may have been the reasons behind the use of MMF in the treatment of autoimmune diseases (AD). But more important than these theoretical considerations is current knowledge of the clinical effects of MMF in patients with AD.

The largest body of evidence exists for its use in the treatment of lupus nephritis; this has been reviewed by Moore and Derry [3]. Randomised trials and cohort studies showed that MMF is as effective, or even more effective, than cyclophosphamide in induction of remission in these patients. This is a milestone in the therapy of lupus nephritis, because MMF, in contrast to cyclophosphamide, does not cause amenorrhoea and infertility in the often young female lupus patients. However, there are still concerns about the design and patient selection of published trials, and in selected cases some physicians may still prefer to give cyclophosphamide precedence over MMF. For indications other than lupus nephritis no randomised controlled trials have been published so far, and the evidence derives from uncontrolled prospective trials or from retrospective case series. Response to MMF has been most frequently reported in patients with systemic sclerosis (SSC), myositis and antineutrophil cytoplasmatic antibodies (ANCA) associated vasculitides. Many of those series are reviewed by Bandelier and colleagues in this issue of the journal [4]. In the same article they describe their own impressive results with the use of MMF in patients with AD, and show, by retrospective chart review, that from 11 pre-treated patients with various connective tissue diseases at least 10 responded to therapy with MMF.

What do we learn from these reports? When should we treat our patients with MMF? Despite the accumulation of promising data on the use of MMF in patients with AD, real evidence exists only for lupus nephritis. There is hope that MMF could be of value in patients with SSC, a disease with very limited therapeutic options, and the same goes for the inflammatory muscle diseases. Here data on steroid sparing immunosuppressive drugs, or on regimens for refractory patients, are largely lacking.

Until we receive results from prospective controlled trials for drugs (as in this case MMF) for potential new indications, we cannot distinguish between real hope for our patients and mere "hype" for a new drug. For MMF the first trials are under way. For patients with small vessel vasculitides the EUVAS study group compares MMF with cyclophosphamide for induction therapy (www.vasculitis.org). In addition, several trials are actively recruiting and, amongst other indications, MMF is being studied for patients with autoimmune hepatitis, SSC and adult Schoenlein-Hennoch purpura (http://clinicaltrials.gov/).

Finally, there is hope that these trials will confirm the first positive reports on the use of MMF in patients with AD.

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References

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