Evidence for efficacy of a drug widely used without authorisation in multiple sclerosis: mycophenolate mofetil

Jun-ichi Kira

Mycophenolate mofetil (MMF) is an oral DNA base synthesis inhibitor that has profound immunosuppressive effects on activated T cells, B cells and macrophages. MMF selectively inhibits inosine 5′-monophosphate dehydrogenase type II, responsible for de novo synthesis of the purine nucleotide guanine. The drug has been used for anti-rejection therapy in organ transplantation and also for immunotherapy in a myriad of autoimmune diseases, including refractory multiple sclerosis (MS). The efficacy of MMF has been examined in several preliminary prospective studies using relatively small numbers of active relapsing–remitting MS patients, in which MMF was introduced as an add on therapy for interferon β.1–5 These studies mostly showed a favourable trend for MMF in reducing the annualised relapse rate (ARR) or cumulative combined active lesion number, although statistically significant effects were hardly confirmed owing to the small sample sizes. MMF monotherapy was also investigated in small uncontrolled studies, resulting in equivocal outcomes.6 Therefore, evidence for MMF in MS remains to be established.

Michel et al7 analysed the efficacy of MMF in the largest ever number of MS patients (344 patients) in a multicenter collaborative study, and found that MMF exerted many statistically significant beneficial effects, such as ARR reduction (from 1.11 to 0.35) (in press). The Expanded Disability Status Scale of Kurtzke scores were also stabilised over 1 year after MMF initiation. Although many adverse events were observed, including gastrointestinal symptoms (diarrhoea, nausea and abdominal pain), benign infectious diseases, insomnia, asthenia and transient lymphopenia, MMF was generally well tolerated. Among the cohort, nearly half of the patients had previously been treated with another immunosuppressive drug and still had a high ARR, suggesting that highly active MS patients were targets for MMF. Nonetheless, MMF was found to be significantly efficacious for reducing ARR in both immunosuppressive treated and untreated subgroups. Thus the present results would provide a rationale for usage of this drug widely administered without authorisation in MS.

However, there are several issues to be considered apart from the retrospective nature of the study. First, the study population was a mixture of various types of MS, including secondary progressive MS, comprising 37.5%, and primary progressive MS, comprising 17.7%. Generally speaking, in primary progressive MS, there are usually no or very few relapses superimposed on the chronic progressive course. In addition, in secondary progressive MS, relapses are infrequent and become less and less frequent as disease duration becomes longer. Given that more than half of the present patients had chronic progressive MS, it might be inappropriate to adopt the ARR as the primary outcome measure to determine MMF efficacy, at least for patients with chronic progressive MS. Second, MMF treatment was stopped in 122 patients (35%) in the present cohort. Given the very high rate of MMF discontinuation, usage of the drug would be quite limited. Third, stabilisation of worsening of the Expanded Disability Status Scale scores should be examined for much longer periods to draw a conclusion about the favourable influence of MMF on chronic progression. With these reservations in mind, the present study would suggest a practical position for MMF in the current unmet need for MS treatment, as a second-line or third-line therapy for refractory MS.

Competing interests None.

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