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Perspectives on maintenance therapy in lupus nephritis

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Abstract

Maintenance immunosuppressive drug therapy is necessary to counter the propensity of lupus nephritis to relapse. Claims that mycophenolate mofetil might be the magic bullet for both induction and maintenance therapies merit critical reappraisal due to inconsistent evidence of the superiority of mycophenolate mofetil over azathioprine, as well as its inordinately greater cost.

Lupus nephritis is among the most challenging complications of systemic lupus erythematosus (SLE). While modern therapies offer the prospect of inducing remission of SLE and lupus nephritis, achieving a complete cure (that is, the disappearance of autoantibodies and sustained clinical remission without ongoing immunosuppressive therapy) is exceptional, occurring in less than 5% of patients. Several therapeutic options, including combinations of high-dose corticosteroids and cyclophosphamide or mycophenolate mofetil, have been shown to be effective in inducing remission within several months.^{1,2} The seminal studies by Donadio *et al.* showed that remissions achieved with 6 months of adjunctive cyclophosphamide were sustained for longer than those achieved with corticosteroids alone, but similar rates of late relapse and progressive renal failure cast doubt on the enduring value of short courses of cyclophosphamide.³ A subsequent controlled trial by Boumpas *et al.* showed that an extended course of low-intensity maintenance therapy was necessary to consolidate the benefits of cyclophosphamide induction therapy for lupus nephritis.⁴ During the same era, empiric practice developed (particularly in European countries) to use azathioprine as maintenance therapy for both lupus nephritis and renal vasculitis.

Contreras *et al.* were among the first to prospectively compare the effectiveness of alternative maintenance therapies following cyclophosphamide-induced remission of lupus nephritis.⁵ These investigators randomized patients in various stages of remission to maintenance therapy with quarterly pulse cyclophosphamide, azathioprine or mycophenolate mofetil. Provocative results suggested that both azathioprine and mycophenolate mofetil were more effective than quarterly pulse cyclophosphamide in preventing relapse, progressive renal failure and death. Critics of these results were concerned that the rates of adverse outcomes were substantially higher than those observed in previous studies and suggested the possibility that demographic factors may have led to the unanticipated results.

The recent international trial reported by Dooley *et al.* directly compared azathioprine and mycophenolate mofetil as maintenance therapies for lupus nephritis.⁶ The investigators

Competing interests

The author declares no competing interests.

randomly assigned 227 patients to one of these agents after the induction of initial remission. Treatment failure rates were approximately twofold higher in the group treated with azathioprine than in the group receiving mycophenolate mofetil maintenance therapy ($P = 0.003$).

Contrary to these results are the findings from the multicenter European MAINTAIN Nephritis Trial, which cast doubt on the position that mycophenolate mofetil provides superior efficacy over azathioprine as maintenance therapy in lupus nephritis.⁷ The MAINTAIN Trial results showed no significant differences in either rates of renal flares or in the evolution of renal biopsy changes (based on changes in activity or chronicity scores) in the group treated with mycophenolate mofetil compared with the group treated with azathioprine.

Comparative studies on the relative immunosuppressive capacities of mycophenolate mofetil and azathioprine for post-transplantation maintenance regimens and for the treatment of other glomerular diseases are informative, although immunologic mechanisms are distinct from those involved in the pathogenesis of lupus nephritis. Indeed, FDA approval of mycophenolate mofetil for antirejection therapy was based on the fact that acute rejection rates were lower than those observed with adjunctive azathioprine therapy. The fact that the half-life of renal allografts was not commensurately improved by mycophenolate mofetil therapy is provocative. Further challenges to the claims that mycophenolate mofetil is advantageous over azathioprine were presented by Remuzzi *et al.*, who reported results from a controlled trial comparing azathioprine and mycophenolate mofetil as adjuncts to steroids and calcineurin inhibitors in renal allograft recipients.⁸ These investigators found no significant differences in allograft function between groups and, in light of the more than tenfold greater costs of mycophenolate mofetil over azathioprine maintenance therapy, they suggested that there was weak if any justification for the common transplant practice favoring mycophenolate mofetil over azathioprine as adjunctive antirejection therapy. Finally, a recent analysis of transplant registry data also indicates that the rates of renal allograft failure from recurrent glomerular disease are the same whether mycophenolate mofetil or azathioprine is used as anti rejection maintenance therapy.⁹

“...achieving a complete cure ... is exceptional, occurring in less than 5% of patients”

Because humoral immune mechanisms are known to be involved in both lupus nephritis and in several forms of renal vasculitis, results of studies of maintenance immunosuppression in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis may offer relevant information. In this regard, a recent study by Hiemstra *et al.* in patients with ANCA-associated renal vasculitis showed that azathioprine is not just equivalent to, but is actually superior to, mycophenolate mofetil maintenance therapy as measured by relapse-free renal survival.¹⁰

Should the above findings showing overlapping effects of mycophenolate mofetil and azathioprine be surprising? Not when one considers the fact that they both function as purine antimetabolites, though by different pharmacologic mechanisms. The active metabolite of mycophenolate mofetil, mycophenolic acid, preferentially binds to inosine monophosphate dehydrogenase, an enzyme that converts inosine to guanosine and is necessary for normal DNA synthesis. In the case of azathioprine, its active metabolite, 6-mercaptopurine, leads to the intercalation of a fraudulent thioguanine nucleotide that in turn impairs subsequent DNA replication. Impairment of purine metabolism by either mechanism has major effects on the proliferation of activated T lymphocytes, and to a lesser extent, B lymphocytes, although neither mechanism seems to have direct effects on autoantibody-producing mature plasma cells.

Mycophenolic acid was discovered in 1913 as a natural product of certain fungi. It was studied first for its antibacterial effects and later in the mid-1900s for its potential immunosuppressant properties, including in some pilot clinical studies in arthritis and psoriasis. Interestingly, zeal for developing this compound waned for a few decades until a new conjugate, mycophenolate mofetil, was synthesized and studied in preclinical models of autoimmunity in the 1970s. It was brought to market in the 1990s following FDA approval based on evidence of its superiority over azathioprine in reducing the risk of acute allograft rejection episodes. Interest soon followed for its application to multiple autoimmune disorders and particularly as a less toxic alternative to cyclophosphamide therapy. Indeed, some enthusiasts entertained the prospect that mycophenolate mofetil would likely show superior efficacy to both cyclophosphamide and azathioprine, a perspective that has not been realized, despite a plethora of editorial commentaries to this effect. Placed in historical context, mycophenolate mofetil seems to fall in line with the typical lifecycle of new scientific discoveries showing changes in a hypothetical 'enthusiasm index' over time (Figure 1). According to this scheme, new treatment options are typically embraced by a burst of enthusiasm based on subjective impressions of efficacy. This phase is typically followed by a period of doubt, based on results of objective, controlled studies; demonstrating the true position of the agent in the therapeutic armamentarium often requires careful balancing of the evidence for efficacy, toxicity and cost of the product. Such is the case with mycophenolate mofetil, where its less than originally conceived efficacy, its more than originally conceived toxicity (not discussed here), and certainly its inordinately burdensome costs leave its ultimate ranking among the choices of immunosuppressive agents in substantial doubt.

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Figure 1.

Hypothetical life-cycle of a new drug. New therapeutic agents often enjoy initial phases of high enthusiasm owing to prescriber anticipation and biased assessments. The overstatement of zealots is commonly offset by a plummet in enthusiasm due to equally unfounded biases of therapeutic nihilists. The ultimate, justifiable level of enthusiasm for a drug is typically acquired in small increments and requires the thoughtful synthesis of objective measures of benefits, risks and costs. This figure is adapted from one by Yolken, R. H. that depicts the hypothetical life-cycle of a new diagnostic assay. Permission obtained from Elsevier Ltd © Yolken, R. H. Nucleic acids or immunoglobulins: which are the molecular probes of the future? *Mol. Cell. Probes* 2, 87-96 (1988).