Is Mycophenolate Mofetil a New Treatment Option in Acute Interstitial Nephritis?

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Interstitial nephritis was recognized as a separate disease in the last quarter of the 19th century. Charcot, in his Lectures on Bright’s Disease of the Kidneys (1), discussed it at length, indicating that because death occurred at the end of a long period, the early (acute) phase of the disease could be evaluated only in autopsies from patients who died accidentally. From microscopic studies of these cases, he concluded that the acute phase was characterized by infiltration of cells that “depending on the theory adopted, are called leukocytes or embryonic cells” while the tubular epithelium was initially healthy, only to be dilated, damaged, and involved in “fibrillar connective tissue” in later stages of the disease. Nevertheless, it is usually accepted that acute interstitial nephritis (AIN) first was recognized as a distinct entity by Councilman (2), as a postinfectious complication of diphtheria and scarlet fever. Since then, AIN has been reported in a vast number of infectious and systemic diseases, and it has been shown to be caused by an ever-increasing number of drugs, notably antibiotics, nonsteroidal anti-inflammatory agents, analgesics, H2 antagonists, anticonvulsants, and hypouricemic agents. It is a relatively uncommon condition that represents 2 to 3% of all renal biopsies (3–5), but its annual incidence seems to be rising (5). In cases of acute renal failure, the incidence of AIN is 7 to 15% (4,6). Definite diagnosis depends on biopsy findings. Prebiopsy diagnosis is suspected in only 60% of cases (7), which is not surprising because the constitutional symptoms of fever, rash, and arthralgias are present in <15% of the cases (7,8), and the other hallmark features described in the initial reports of methicillin-induced AIN, such as eosinophilia and eosinophiluria, rarely are present in other drug-related cases (6).

In contrast to the good prognosis reported in early series after removal of the causal agent (9–11), recent studies have shown that serum creatinine remains elevated in 40% of cases (6). Methylprednisolone bolus followed by oral prednisone is a generally accepted but far from proved treatment option in patients who do not show improvement in renal function 10 to 15 d after discontinuation of the drug that is responsible for AIN. Scarce information exists on alternative treatments in patients who do not respond to steroids or in those who present worsening of renal failure when steroids are discontinued or in whom steroid administration is contraindicated. It is in eight patients in these categories that Preddie et al. report the results of treatment with mycophenolate mofetil (MMF) in this issue of CJASN.

The rationale for using MMF as an alternative treatment in steroid-resistant or steroid-dependent AIN is based on the prevailing view that most, if not all, AIN in humans result from cell-mediated immune reactivity (6), and MMF is a drug with a relatively large therapeutic window that has proved useful in human transplantation as well as in a variety of immune-related conditions (12).

Of the eight patients who were treated by Preddie et al., renal function improved in five patients, and none is taking steroids after 6 mo of MMF treatment. These are impressive results in this subgroup of patients who have AIN, who are more difficult to treat and have a worse long-term prognosis, yet several caveats need to be considered. The number of patients is small, and the study is retrospective. However, as the authors point out, it is unlikely that a single institution would be able to gather enough patients with AIN to do a prospective, randomized, double-blind study of MMF treatment. Therefore, at the present time, the evidence presented by Preddie et al. is the best we have available. The authors state that the use of MMF was reported previously only in abstract form. In addition, there is a very recent report (obviously not available to the authors) that found that MMF induced a sustained remission of sarcoid-associated AIN in a child in whom steroids had to be discontinued because of severe side effects (13).

In the report of Preddie et al., there are some aspects that one wishes would have been discussed more extensively. Most of these aspects relate to the steroid therapy and are important because they would help to define the indications for MMF therapy. In the abstract, the authors state that the eight patients were steroid resistant. Actually, they were steroid dependent or intolerant, as stated in the Results section. Did the patients receive bolus of methylprednisolone and then oral prednisone? How were the steroids tapered? The usual practice in AIN is taper steroids very rapidly after 1 to 2 mo of treatment (6). How long after MMF therapy was started were steroids discontinued, and how were they then tapered? The authors indicate that steroid treatment was maintained for at least 6 mo before the initiation of MMF, and in the table, they show that two patients had two courses of steroids. Were they on a low...
maintenance dose between courses, or were the steroids given intermittently?

In relation to the effects of MMF treatment on renal function, which is the central aspect of the report, the authors report serum creatinine values at the time when MMF was started and at the end of the follow-up, at which time MMF had been stopped 3 to 8 mo previously in five patients. It would have been interesting to know also the serum creatinine values at the end of MMF treatment to evaluate whether renal function continued to improve after MMF was discontinued in patients 1, 2, 3, 5, and 8.

Nevertheless, the article of Preddie et al. suggests that MMF treatment should be considered as an alternative to steroids in a disease such as AIN in which no definite data exist with respect to effective treatment. In fact, the studies that have compared steroid treatment and no treatment have failed to demonstrate beneficial effects of steroids (5,8,14–16). Admittedly, these are retrospective investigations that have failed to modify the opinion based on early reports, also uncontrolled, that steroids improved AIN (6,17). One could posit that a multicenter, prospective, randomized, double-blind study of potential treatments versus no treatment is very much needed in AIN. Surely, a disease that carries a 40% risk for chronic renal disease (6) is well worth the trouble. In the meantime, the article of Preddie et al. gives a reasonable foundation to the use of MMF in patients who have AIN and are unresponsive to, intolerant of, or dependent on steroid therapy.

References