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Editorial

Mycophenolate mofetil to the rescue in autoimmune hepatitis: A fresh sprout on the decision tree ☆

Albert J. Czaja*

Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine, 200 First Street S.W., Rochester, MN 55905, USA

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The concept that some patients with autoimmune hepatitis may not respond well to corticosteroid therapy can be difficult to accept. Success breeds complacency, and few treatments of chronic liver disease have been as successful as corticosteroid therapy. Prednisone alone or a lower dose in combination with azathioprine induces clinical, laboratory and histological improvement in 80% of adults with autoimmune hepatitis within 3 years [1–4], normalizes 10- and 20-year life-expectancies [5], and prevents or reduces hepatic fibrosis in 79% [6]. Similar but less comprehensive results have been reported in children [7–9], and expectations of treatment success are justifiably high in both patient populations. The report by Aw and colleagues that 14% of children fail to respond or tolerate corticosteroid treatment [10] complements the experience in adults [11,12], and it is an important reality check. Not only does it re-confirm the need for a rescue therapy in autoimmune hepatitis, but it also strengthens the support for mycophenolate mofetil in this role [10].

Mycophenolate mofetil is a prodrug hydrolyzed by liver esterases to produce the active metabolite, mycophenolic acid, which in turn acts as a non-competitive, reversible inhibitor of inosine monophosphate dehydrogenase [13–16]. Inosine monophosphate dehydrogenase is the rate-limiting enzyme for *de novo* synthesis of purines, and by inhibiting its action, mycophenolate mofetil selectively prevents the proliferative responses of T and B cells to antigens. Mycophenolate mofetil is a purine antagonist like azathioprine, but its potent immunosuppressive actions and independence from the thiopurine methyltransferase pathway of catabolism enhance its appeal as a more powerful and better tolerated agent than azathioprine [13–16].

Aw and colleagues indicate that 18 of 26 children with problematic autoimmune liver disease (69%) had complete or partial laboratory resolution after therapy with mycophenolate mofetil and that all were alive 3.5–7.6 years (median, 6.7 years) from the onset of treatment [10]. These frequencies of improvement and transplant-free survival are presumably greater than would have been expected if mycophenolate mofetil had not been instituted, and they are similar to the outcomes in adults who have been treated with the same drug under comparable clinical circumstances [17–24]. Improvements of varying degree and nature have occurred in 31–84% of similarly distressed and treated adults [17–24].

Nine small, single-institution, retrospective experiences now support the use of mycophenolate mofetil as a second-line treatment for autoimmune hepatitis [10,17–24]. The number and size of these studies attest to the rarity of refractory disease in single institutions, the difficulty of performing rigorous treatment trials in this select patient population, and the urgent need for rescue therapy. This latter aspect of patient care can trump the call (and wait) for collaborative prospective treatment trials, and mycophenolate mofetil is already infiltrating the therapeutic arsenal of autoimmune hepatitis [17]. As Aw and colleagues wisely recommend,

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* Tel.: +1 507 2848118; fax: +1 507 2840538.
E-mail address: czaja.albert@mayo.edu

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mycophenolate mofetil should be studied further in randomized clinical trials [10], but the reality of clinical practice threatens to supersede this advice [17].

The off-label institution of therapy with mycophenolate mofetil is a bold step. The unorthodoxy and empiricism of the treatment are commonly compounded with inexperience in its administration. Accordingly, the decision for off-label treatment demands a sober, highly individualized analysis, preferably by an experienced hepatologist in a tertiary medical center, ideally within the context of a clinical trial. The appropriate target population, dosing schedule, monitoring sequence, and safety profile are uncertain, and even the event that requires rescue is unclear.

The minimum level of residual disease activity that is tolerable long term is uncertain in autoimmune hepatitis, and treatment with mycophenolate mofetil for an incomplete response to corticosteroid therapy may not represent a true salvage situation. Mild liver inflammation can be non-progressive if conventional therapy is continuous and dose-adjusted to disease behavior [25,26]. Disease progression rather than controlled persistence may be the most appropriate signal for rescue.

Similarly, a patient's intolerance of one medication does not imply that the introduction of another less established, more expensive drug will ameliorate the situation. Six to 34% of adults in need of rescue are unable to tolerate mycophenolate mofetil because of nausea, headache, vomiting, pancreatitis, rash, alopecia, deep venous thrombosis, and diarrhea [22–24], and 13 of 26 children treated by Aw and colleagues [10] experienced side effects, including four in whom the medication had to be stopped (15%), presumably because of leukopenia and neutropenia.

Combined results from the four most recent reports indicate that treatment with mycophenolate mofetil is complicated by drug intolerance in 18% and an incomplete or non-response in 50% [10,21–24]. These findings underscore the need for codified indications for salvage therapy and confident dosing schedules before this treatment can be designated appropriate and safe. Mycophenolate mofetil is 6–14 times more expensive than azathioprine [27–29], and its inconsistent record of efficacy and safety argue for discretion and precaution in its off-label use [10,21–24].

Progress has been made in identifying patients with autoimmune liver disease who will not respond to therapy with mycophenolate mofetil, but additional characterizations are necessary to target the treatment and conserve resources. Six of the 8 children in the study of Aw and colleagues who could not be rescued by mycophenolate mofetil had autoimmune sclerosing cholangitis [10]. This experience in children is similar to that in adults with primary sclerosing cholangitis [30,31], and it should avert the fruitless administration of an expensive, potentially toxic, medication to this subgroup.

Hennes and colleagues also provide guidelines in selecting the adult subset best suited for rescue with mycophenolate mofetil [23]. Six of 8 adults with prior non-response to azathioprine could not be rescued with mycophenolate mofetil, whereas 12 of 28 patients (43%) with intolerance to azathioprine improved [23]. In this experience, patients were rescued from their original medication rather than their liver disease. Additional analyses of a similar nature are necessary to optimize the use of mycophenolate mofetil in autoimmune hepatitis. They promise to improve the efficacy of the drug by restricting its use. As the number of candidates for rescue with mycophenolate mofetil shrinks, an urgent call for other rescue agents can be anticipated.

The study by Aw and colleagues underscores the need for rescue therapy in autoimmune hepatitis, and it defines the subset of children in whom mycophenolate mofetil is likely to help [10]. It also highlights the importance of an evolving area of investigation in autoimmune hepatitis where the deficiencies of conventional therapy are recognized and new options for distressed subgroups are developed. This area must be fortified so that collaborative investigative networks can be nurtured and new treatments can be evaluated quickly and reliably. Mycophenolate mofetil must earn a place in the treatment algorithm for both children and adults with autoimmune hepatitis by organized prospective clinical trials rather than acclamation. Until then, its branch on the decision tree is fragile.

References

[1] Kanzler S, Lohr H, Gerken G, Galle PR, Lohse AW. Long-term management and prognosis of autoimmune hepatitis (AIH): a single center experience. Z Gastroenterol 2001;39:339–348.
[2] Floreani A, Niro G, Rosa Rizzotto E, Antoniazzi S, Ferrara F, Carderi I, et al. Type 1 autoimmune hepatitis: clinical course and outcome in an Italian multicentre study. Aliment Pharmacol Ther 2006;24:1051–1057.
[3] Seo S, Toutounjian R, Conrad A, Blatt L, Tong MJ. Favorable outcomes of autoimmune hepatitis in a community clinic setting. J Gastroenterol Hepatol 2008;23:1410–1414.
[4] Czaja AJ. Rapidity of treatment response and outcome in type 1 autoimmune hepatitis. J Hepatol 2009;51:161–167.
[5] Roberts SK, Therneau T, Czaja AJ. Prognosis of histological cirrhosis in type 1 autoimmune hepatitis. Gastroenterology 1996; 110:848–857.
[6] Czaja AJ, Carpenter HA. Decreased fibrosis during corticosteroid therapy of autoimmune hepatitis. J Hepatol 2004;40:644–650.
[7] Gregorio GV, Portmann B, Reid F, Donaldson PT, Doherty DG, McCartney M, et al. Autoimmune hepatitis in childhood. A 20 year survey. Hepatology 1997;25:541–547.
[8] Yachha SK, Srivastava A, Chetri K, Saraswat VA, Krishnani N. Autoimmune liver disease in children. J Gastroenterol Hepatol 2001;16:674–677.
[9] Saadah OI, Smith AL, Hardikar W. Long-term outcome of autoimmune hepatitis in children. J Gastroenterol Hepatol 2001;16:1297–1302.
[10] Aw MM, Dhawan A, Samyn M, Bargiota A, Mieli-Vergani G. Mycophenolate mofetil as rescue treatment for autoimmune liver

disease in children: A 5-year follow-up. J Hepatol 2009;51: 156–160.
[11] Montano-Loza AJ, Carpenter HA, Czaja AJ. Features associated with treatment failure in type 1 autoimmune hepatitis and predictive value of the model of end stage liver disease. Hepatology 2007;46:1138–1145.
[12] Czaja AJ. Features and consequences of untreated autoimmune hepatitis. Liver Int 2008 Oct 14. [Epub ahead of print].
[13] Becker BN. Mycophenolate mofetil. Transplant Proc 1999;31:2777–2778.
[14] Allison AC, Eugui EM. Mycophenolate mofetil and its mechanisms of action. Immunopharmacology 2000;47:85–118.
[15] Cohn RG, Mirkovich A, Dunlap B, Burton P, Chiu SH, Eugui E, et al. Mycophenolate acid increases apoptosis, lysosomes and lipid droplets in human lymphoid and monocytic cell lines. Transplantation 1999;68:411–418.
[16] Mehling A, Grabbe S, Voskort M. Mycophenolate mofetil impairs the maturation and function of murine dendritic cells. J Immunol 2000;165:2374–2381.
[17] Czaja AJ, Carpenter HA. Empiric therapy of autoimmune hepatitis with mycophenolate mofetil: comparison with conventional treatment for refractory disease. J Clin Gastroenterol 2005;39:819–825.
[18] Richardson PD, James PD, Ryder SD. Mycophenolate mofetil for maintenance of remission in autoimmune hepatitis patients resistant to or intolerant of azathioprine. J Hepatol 2000;33:371–375.
[19] Devlin SM, Swain MG, Urbanski SJ, Burak KW. Mycophenolate mofetil for the treatment of autoimmune hepatitis in patients refractory to standard therapy. Can J Gastroenterol 2004;18:321–326.
[20] Chatur N, Ramji A, Bain VG, Ma MM, Marotta PJ, Ghent CN, et al. Transplant immunosuppressive agents in non-transplant chronic autoimmune hepatitis: the Canadian Association for the Study of Liver (CASL) experience with mycophenolate mofetil and tacrolimus. Liver Int 2005;25:723–727.
[21] Inductivo-Yu I, Adams A, Gish RG, Wakil A, Bzowej NH, Frederick RT, et al. Mycophenolate mofetil in autoimmune hepatitis patients not responsive or intolerant to standard immunosuppressive therapy. Clin Gastroenterol Hepatol 2007;5:799–802.
[22] Hlivko JT, Shiffman ML, Stravitz RT, Luketic VA, Sanyal AJ, Fuchs M, et al. A single center review of the use of mycophenolate mofetil in the treatment of autoimmune hepatitis. Clin Gastroenterol Hepatol 2008;6:1036–1040.
[23] Hennes EM, Oo YH, Schramm C, Denzer U, Buggisch P, Wiegard C, et al. Mycophenolate mofetil as second line therapy in autoimmune hepatitis? Am J Gastroenterol 2008;103: 3063–3070.
[24] Wolf DC, Bojito L, Facciuto M, Lebovics E. Mycophenolate mofetil for autoimmune hepatitis: a single practice experience. Dig Dis Sci, 2008 Dec 12 [Epub ahead of print].
[25] Czaja AJ. Low dose corticosteroid therapy after multiple relapses of severe HBsAg-negative chronic active hepatitis. Hepatology 1990;11:1044–1049.
[26] Johnson PJ, McFarlane IG, Williams R. Azathioprine for long-term maintenance of remission in autoimmune hepatitis. N Engl J Med 1995;333:958–963.
[27] Seikaly MG. Mycophenolate mofetil-is it worth the cost? The in-favor opinion. Pediatr Transplant 1999;3:79–82.
[28] Heneghan MA, Al-Chalabi T, McFarlane IG. Cost-effectiveness of pharmacotherapy for autoimmune hepatitis. Expert Opin Pharmacother 2006;7:145–156.
[29] Tse KC, Tang CS, Lam MF, Yap DY, Chan TM. Cost comparison between mycophenolate mofetil and cyclophosphamide-azathioprine in the treatment of lupus nephritis. J Rheumatol 2009;36:76–81.
[30] Sterling RK, Savatori JJ, Luketic VA, Sanyal AJ, Fulcher AS, Stravitz RT, et al. A prospective, randomized-controlled pilot study of ursodeoxycholic acid combined with mycophenolate mofetil in the treatment of sclerosing cholangitis. Aliment Pharmacol Ther 2004;20:943–949.
[31] Talwalkar JA, Angulo P, Keach JC, Petz JL, Jorgensen RA, Lindor KD. Mycophenolate mofetil for the treatment of primary sclerosing cholangitis. Am J Gastroenterol 2005;100:308–312.