Lower 12-hour Trough Concentrations of Mycophenolic Acid in Patients with Active Systemic Vasculitides Taking Mycophenolate Mofetil

To the Editor:

Mycophenolic acid (MPA), the active form of mycophenolate mofetil (MMF), is an immunosuppressant increasingly used for remission maintenance after induction therapy for systemic lupus erythematosus (SLE) and antineutrophil cytoplasmic antibody-associated vasculitides (AAV)[1,2]. However, no recommendations concerning optimal dose of MMF for AAV are available, and a high relapse rate might compromise its use as a first-line remission-maintenance therapy[3]. An association between SLE activity and the pharmacokinetics of MPA has been described[4,5,6]. We previously reported that, for patients with SLE without renal manifestations, clinical flares under MMF were associated with 12-h trough concentrations (C_{12h}) of MPA that were < 3 mg/l[5]. Pertinently, the increasing attention on therapeutic drug-monitoring for SLE raises the question of individualizing MMF therapy for patients with vasculitides based on its pharmacokinetics. Although preliminary results suggest MMF-pharmacokinetic efficacy relationships in AAV[4], further confirmatory data are needed.

We conducted a single-center observational study to investigate the relationships between plasma MPA exposure and disease activity in 28 patients with only extrarenal manifestations of systemic vasculitides, defined according to the 1992 Chapel Hill Consensus Conference[7]. The main indication for starting MMF was remission maintenance after induction therapy with pulse cyclophosphamide. Patients with active renal involvement (proteinuria > 0.5 g/24 h with urinary casts and/or hematuria), renal impairment (glomerular filtration rate < 60 ml/min/1.73 m^2), and/or liver dysfunction were not included. Patients who were included had been taking a stable MMF dose 1–3 g/day for ≥ 1 month and a stable oral prednisone dose for ≥ 15 days. Efficacy was assessed after at least 6 months of MMF use. At inclusion, remission was defined as Birmingham Vasculitis Activity Score[8] (BVAS) = 0, indicating no persistently active disease manifestations since the previous examination 1 month earlier[3], and classifying patients as therapeutic successes. Patients whose disease was not controlled (BVAS ≥ 1) were considered failures. MPA C_{12h} and areas under the time-plasma concentration curve between 0 and 12 h ($AUC_{0–12h}$) were determined[9], and biological characteristics and oral prednisone dose (range 5–45 mg/day) were recorded (Table 1). All patients tolerated MMF well and were compliant. Successes (n = 20) had significantly higher MPA C_{12h} than failures (n = 8) and tended to have higher MPA $AUC_{0–12h}$ (Figure 1).

Hiemstra, *et al* conducted the first randomized controlled study of MMF therapy for AAV with longterm followup: contrary to what was initially thought, MMF at a starting fixed dose of 2 g/day, reduced to 1 g/day and withdrawn after 42 months, was less effective than azathioprine for maintaining remission[3]. That observation compromises its use as first-line maintenance therapy. Nevertheless, a drug's lower efficacy must be interpreted with caution, as it perhaps reflects a nonoptimized therapeutic schedule. In our study, active disease was associated with a significantly lower MPA C_{12h}, suggesting that therapeutic drug monitoring in vasculitis patients with dose adaptation would probably improve their outcomes over a fixed-dose strategy. Such monitoring was previously recommended for patients with SLE, whose routine MPA C_{12h} measurements could predict their clinical outcomes[4,5].

The limitations of our study (small number of patients, absence of randomization because of retrospective study design, single-center participa-

Table 1. Characteristics of the 28 patients and therapeutic responses (univariate analysis).

Characteristic	All Patients, n = 28	Successes, n = 20	Failures, n = 8	p*
Clinical				
Polyarteritis nodosa, n	9			
Wegener's granulomatosis**, n	8			
Churg-Strauss syndrome***, n	5			
Microscopic polyangiitis, n	4			
Other vasculitis syndrome, n	2			
ANCA-positive, n (%)†	19 (67)			
BVAS	0 (0–4)	0 (0–0)	4.5 (4–5)	0.0003
Demographic				
Females/males, n	10/18	7/13	3/5	0.57††
Age, yrs	50 (20–54)	53 (50–59)	47 (20–50)	0.30
Body weight, kg	72.5 (65–85)	72.5 (66–82)	74 (60–82)	0.62
Biological				
GFR, ml/min/1.73 m^2	80 (74–133)	79 (74–83)	81 (72–85)	0.64
Albumin, g/l	43.5 (38.4–44.5)	41.3 (38–44)	47.6 (45–49)	0.28
Treatment				
MMF, g/day	2 (2–2)	2 (2–2)	2 (2–2)	0.7
Months of MMF therapy, n	10 (6–12)	12 (6–12)	9 (6–12)	0.5
Corticosteroids, mg/day	10 (5–20)	10 (5–12)	32 (11–45)	0.09
MPA pharmacokinetics				
$AUC_{0–12h}$, mg•h/l	56 (37.4–80.8)	65.7 (40.5–81.3)	34.8 (28.2–55)	0.09
C_{12h}, mg/l	2.8 (1.3–4.3)	2.9 (1.7–4.9)	1.3 (0.9–1.7)	0.02
Correlations#				
$AUC_{0–12h}$ and C_{12h}	r = 0.78, p = 0.0001#			
$AUC_{0–12h}$ and prednisone dose	r = –0.18, p = 0.46#			

Values are expressed as medians (interquartile range) unless otherwise stated. * Mann-Whitney U test. ** Granulomatosis with polyangiitis. *** Eosinophilic granulomatosis with polyangiitis. † By indirect immunofluorescence or enzyme-linked immunosorbent assay. †† Fisher exact test. # Spearman correlation test. AUC: area under the curve; BVAS: Birmingham Vasculitis Activity Score; GFR; glomerular filtration rate, Cockcroft-Gault formula; MMF: mycophenolate mofetil; MPA: mycophenolic acid; ANCA: antineutrophil cytoplasmic antibody.

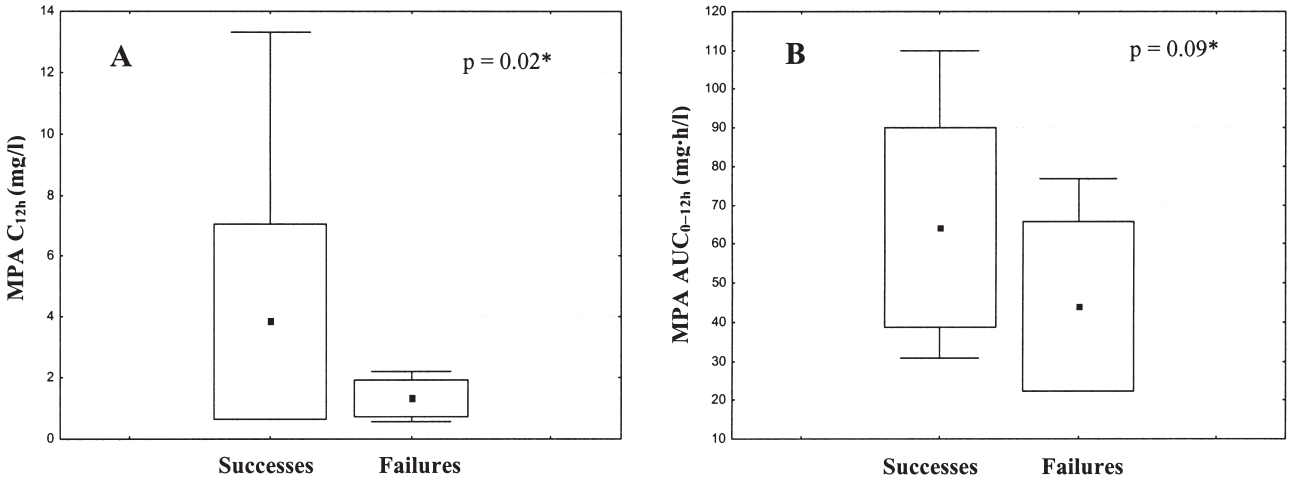

Figure 1. Baseline pharmacokinetic measures of mycophenolic acid (MPA) for therapeutic successes and failures. A. MPA 12-h trough concentrations. B. Area under the time-plasma concentration curves for MPA between 0 and 12 h. Squares inside the boxes indicate the means, lower and upper box limits are SD, and T-bars correspond to the range. *Mann-Whitney U test.

tion) might explain why no association was observed between therapeutic response and variables other than pharmacokinetics. Consequently, we were not able to identify confounding variables in a multivariate analysis, even though several factors are likely to be responsible for low MPA concentrations: renal function, albumin levels, and prednisone doses significantly influence plasma concentrations of the main MPA glucuronide metabolite, and thus drug clearance[10]. However, our restricted inclusion criteria (a population relatively homogeneous for renal and hepatic functions, no patient with hypoalbuminemia) prevented bias in the pharmacokinetic results, and it is notable that, despite the small sample size, highly significant pharmacokinetic results were obtained.

The possible influence of prednisone on disease outcome and pharmacokinetics merits consideration. Although they were not significant, higher prednisone doses were recorded for the treatment failures. This observation merely reflected routine clinical practices, i.e., usually increasing steroid doses as salvage therapy, rather than optimizing MMF doses. Thus, intensified prednisone may lower MPA concentrations by stimulating its metabolism[10]; however, prednisone doses and MPA exposure were not correlated (Table 1), potentially excluding the influence of prednisone on pharmacokinetics and clinical outcome as a confounding factor.

Despite the lack of statistical power, we observed wide interpatient variability of MPA pharmacokinetics in our study group, as previously described in SLE, and showed that active disease was associated with lower MPA concentrations, thus encouraging further concentration-controlled randomized control trials in larger populations with vasculitides. Should such relationships be firmly proven, given the strong correlation we observed between MPA $AUC_{0–12h}$ and C_{12h} (Table 1), therapeutic drug monitoring could also be based on a single measurement 12 h post-dosing. The MPA C_{12h} efficacy threshold would remain to be defined. All our patients judged to be therapy failures had $C_{12h} < 2.5$ mg/l. Conversely, all patients with higher C_{12h} values had sustained remissions. That value, which is very close to the preliminary efficacy threshold found for SLE and AAV patients (3–3.5 mg/l)[4,5], could be included in a first-guidance protocol for therapeutic drug-monitoring of MMF in such patients.

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REFERENCES

1. Hiemstra TF, Jayne D. Newer therapies for vasculitis. Best Pract Res Clin Rheumatol 2009;23:379-89.
2. Hiemstra TF, Jones RB, Jayne DRW. Treatment of primary systemic vasculitis with the inosine monophosphate dehydrogenase inhibitor mycophenolic acid. Nephron Clin Pract 2010;116:1-10.
3. Hiemstra TF, Walsh M, Mahr A, Savage CO, de Groot K, Harper L, et al, for the European Vasculitis Study Group (EUVAS). Mycophenolate mofetil vs azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis: A randomized controlled trial. JAMA 2010;304:2381-8.
4. Neumann I, Fuhrmann H, Fang IF, Jaeger A, Bayer P, Kovarik J. Association between mycophenolic acid 12-h trough levels and clinical endpoints in patients with autoimmune diseases on mycophenolate mofetil. Nephrol Dial Transplant 2008;23:3514-20.
5. Djabarouti S, Breilh D, Duffau P, Lazaro E, Greib C, Caubet O, et al. Steady-state mycophenolate mofetil pharmacokinetic parameters enable prediction of systemic lupus erythematosus clinical flares: An observational cohort study. Arthritis Res Ther 2010;12:1-7.
6. Zahr N, Arnaud L, Marquet P, Haroche J, Costedoat-Chalumeau N, Hulot JS, et al. Mycophenolic acid area under the curve correlates with disease activity in lupus patients treated with mycophenolate mofetil. Arthritis Rheum 2010;62:2047-54.
7. Jennette JC, Falk RJ, Andrassy K, Bacon PA, Churg J, Gross WL, et al. Nomenclature of systemic vasculitides. Proposal of an International Consensus Conference. Arthritis Rheum 1994; 37:187-92.
8. Luqmani RA, Bacon PA, Moots RJ, Janssen BA, Pall A, Emery P, et al. Birmingham Vasculitis Activity Score (BVAS) in systemic necrotizing vasculitis. QJM 1994;87:671-8.
9. Djabarouti S, Duffau P, Lazaro E, Chapouly C, Greib C, Viallard JF, et al. Therapeutic drug monitoring of mycophenolate mofetil and enteric-coated mycophenolate sodium in patients with systemic lupus erythematosus. Expert Opin Pharmacother 2010;11:689-99.
10. Staatz CE, Tett SE. Clinical pharmacokinetics and pharmacodynamics of mycophenolate in solid organ transplant recipients. Clin Pharmacokinet 2007;46:13-58.

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