

Oral Cyclophosphamide Is on the Verge of Extinction as Therapy for Severe Autoimmune Diseases (Especially Lupus): Should Nephrologists Care?

Lee A. Hebert Brad H. Rovin

Department of Internal Medicine, The Ohio State University Medical Center, Columbus, Ohio, USA

Key Words

SLE nephritis · Oral cyclophosphamide · Intravenous cyclophosphamide

Abstract

Some day we will have powerful targeted therapies for autoimmune diseases. Remission will be induced efficiently. Side effects will be mere ripples. Unfortunately, that day is not imminent. Current therapies are powerful but with unintended targets and side effects that can be equivalent to a sea change. For SLE, the current competition to select the 'gold standard' immunosuppressant has come down to two regimens: intravenous cyclophosphamide (IVCY, standard NIH protocol or its variations) versus oral mycophenolate (MMF). Until recently, IVCY reigned as the gold standard, a title it achieved through a curious journey that did not involve rigorous head-to-head competition. Oral cyclophosphamide (POCY) has not been invited to the current competition to select the gold standard immunosuppressant despite the substantial evidence that POCY can perform at least as well as IVCY or mycophenolate, and compared to IVCY, is far less expensive, easier for the patient, and maybe more effective in African-Americans. Here, we state the case for POCY as therapy for severe autoimmune diseases. We suggest that if POCY is allowed to compete, it will not disappoint.

Copyright © 2010 S. Karger AG, Basel

Introduction

There are unmistakable signs that oral cyclophosphamide (POCY) is on the verge of extinction in the management of autoimmune diseases through no fault of its own. This editorial discusses why we should not let this happen, and what we can do to prevent the untimely and arbitrary extinction of POCY. We begin by addressing the last point.

To avoid extinction, POCY must prove itself worthy by its performance in rigorous, prospective, randomized trials against its chief rivals, intravenous cyclophosphamide (IVCY) and mycophenolate (MMF). Unfortunately, there is resistance to include a POCY arm in clinical trials. A common concern is that POCY is 'too dangerous'. However, this concern is unwarranted. POCY toxicities can be reduced to that of MMF by limiting POCY dose and duration of therapy, as discussed later.

Some may argue that promoting cyclophosphamide therapy in any form is misguided. Instead, we should focus on developing therapies that are equally potent but safer and more targeted. Unfortunately, such therapy is not even on the horizon. The need to identify the gold standard immunosuppressant is particularly pressing for those of African ancestry who often respond less well to either IVCY or MMF than those of European ancestry [1–4].

Defining the role of POCY takes on additional significance because of the current emphasis on comparative-effectiveness studies [5]. As discussed later, compared to IVCY, POCY incurs much less cost and is easier for the patient.

To develop the case for POCY, we pose and answer a series of questions.

What Are the Signs of POCY's Imminent Demise as Acceptable Therapy for Severe SLE Nephritis?

Two recent editorials on the status of lupus nephritis therapy do not even mention POCY [6, 7]. In the most recent meta-analysis comparing MMF and cyclophosphamide therapy in SLE, POCY is mentioned but only to dismiss it because in the randomized trials POCY was used in only 52/456 (11.4%) of the patients. The rest received IVCY [8]. In addition, none of the recent or current multicenter SLE trials (EXPLORER, ALMS, LUNAR, BELONG, APRIL, or ACCESS) include a POCY arm.

With respect to the use of POCY in ANCA-related vasculitis, the future is also discouraging. CYCLOPS, the recently published randomized trial of IVCY versus POCY, concluded that POCY and IVCY provided similar outcomes but IVCY caused fewer episodes of leukopenia. This conclusion, which tilted the playing field in favor of IVCY, was surprising given the trends favoring POCY with regard to ESRD events, preservation of GFR, and relapse rate [9]. Indeed, if the data are made available on trends in proteinuria (proteinuria likely was lower in the POCY cohort because relapse rate was less) and the uncensored trend in eGFR is provided (they censored the GFR trend lines for those who reached ESRD-5 in the IVCY group and only 1 in the POCY group), the conclusion of that work might be changed to favoring POCY over IVCY, as we have suggested [10].

It Is Widely Perceived that IVCY Is Better than POCY in the Management of Severe SLE Nephritis: How Did This Happen?

Although IVCY has reigned as the gold standard [11], it did not acquire its golden reputation in rigorous head-to-head competition [12]. Indeed, until the recently reported EULAR study [13] (discussed later) there had been only one prospective randomized trial comparing IVCY to POCY in lupus. That study conducted by the NIH SLE group, showed no significant difference in outcome be-

tween the patients assigned to IVCY (n = 20) or POCY (n = 18), except that 3 in the POCY cohort developed cystitis. Thus, IVCY was chosen as the favored therapy [14]. However, the relevance of that trial to current practice is minimal because the regimens used (IVCY at 500–1,000 mg/m²/each 3 months for a median of 4 years, or POCY at 1–4 mg/kg/day for a median of 4 years) are far different from the IVCY and POCY regimens presently recommended.

Thereafter, the NIH SLE group studied only IVCY, comparing it to steroid therapy alone [15–18]. It was over this period that the IVCY protocol evolved into its current form (500–750 mg/m² per month for 6 months, then quarterly IVCY for 12–18 months).

The NIH studies of cyclophosphamide therapy of SLE nephritis are landmarks because they establish beyond doubt the importance of immunosuppressive therapy for severe SLE GN. However, those studies do not constitute the basis for deciding the merits of POCY versus IVCY in the therapy of severe SLE GN. The recent EULAR study: 'pulse' cyclophosphamide versus 'continuous' cyclophosphamide in severe SLE nephritis [13], also does not decide the merits of POCY versus IVCY. EULAR found no difference in outcome between the regimens. However, confounding the EULAR interpretation is that the pulse group received about 1/3 more cyclophosphamide than the continuous group. Thus, a plausible interpretation of EULAR is that POCY outperformed pulse therapy because it provided a similar outcome with less cyclophosphamide.

POCY can be expected to be more effective than IVCY because during the induction period, which is likely the most critical interval, the standard POCY regimen provides cyclophosphamide at about a 3-fold greater rate than the standard NIH IVCY protocol. Cyclophosphamide is virtually 100% absorbed from the gastrointestinal tract [19]. Thus, POCY and IVCY doses can be compared directly.

We suggest that the numerous reports of failure of cyclophosphamide to stop progression of SLE GN [1, 20] represent undertreatment because IVCY was used rather than POCY.

What about the Toxicity of POCY Compared to That of IVCY?

Given the difference in cyclophosphamide exposure between the POCY and IVCY regimens it can be readily understood that POCY might have greater toxicity than IVCY. However, as we recently reported [21], the

potential for greater toxicity with POCY than IVCY should be largely avoidable by lower dose, shorter course POCY along with measures for gonadal and bladder protection (discussed later). In addition, the POCY should be reserved for those presenting with severe SLE GN or those experiencing severe relapse of SLE GN. POCY is not recommended for maintenance therapy, even in low dose.

Another ‘toxicity’ is cost. POCY therapy is far less expensive than IVCY (in the United States less than USD 1,000 per course for POCY versus more than USD 9,000 per course for IVCY), and is more convenient. The greater cost and inconvenience of IVCY is incurred because in the USA, UK, and certain other countries, IVCY requires administration in an infusion center and incurs physician charges. A hidden expense is that with each infusion the patient loses a day of work, and sometimes more if lingering symptoms develop [21].

IVCY also has unique toxicities and, although rare, can be severe. They include acute pulmonary failure (cyclophosphamide pneumonitis), and acute bone marrow failure [19]. Also, the risk of cyclophosphamide overdose in those with decreased GFR is greater with IVCY than POCY because only the POCY regimen allows daily dose adjustment. Unrecognized decreases in GFR is particularly a problem in young females whose serum creatinine does not reflect their GFR because of low creatinine production [22, 23] or because of increased tubular secretion of creatinine associated with low serum albumin levels [24]. Another concern is when the patient receives IVCY in error. This occurs when the acutely ill SLE patient receives IVCY on the assumption that severe SLE is present, when the real problem is severe infection. Disastrous consequences can follow [pers. unpubl. obs.].

What Is the Evidence that POCY May Be Better than MMF for Severe SLE Nephritis?

In the only prospective randomized trial comparing POCY to MMF, the therapies were comparable in remission induction rates but the relapse rate was 46% in the MMF group and only 17% in the POCY group ($p = 0.02$) (reviewed in [25]). With regard to the greater toxicity of POCY than MMF noted in that study, we suggest that 6 months of POCY at 2.5 mg/d is more POCY than is needed. It exposes the SLE patient to risk without benefit [21].

A relevant example of administering more cyclophosphamide than is needed is provided by the long-term follow-up of Houssiau’s Euro-Lupus randomized trial of

standard (NIH) IVCY protocol versus a low-dose IVCY protocol [26]. There was no benefit of the high-dose protocol. It only increased risk because of greater exposure to cyclophosphamide.

With regard to MMF versus IVCY in SLE nephritis, as we [27] and others [8] have recently discussed, there is a virtual tie with regard to safety and efficacy.

Should Cyclosporine or Tacrolimus Be Invited to Compete with POCY?

We suggest that calcineurin inhibitors (CNI) should not be used as the sole immunosuppressant for induction therapy in severe SLE GN. The rationale is that what has been interpreted as efficacy of CNI in SLE GN, and in other immune complex-mediated glomerulopathies, may only reflect the ability of this class of drugs to reduce proteinuria by stabilizing podocytes [28]. The underlying mechanism of the GN, immune complex accumulation, may not be affected by CNI [29]. The key details of this interpretation are as follows:

- (1) Proteinuria decreases rapidly when CNI are administered to patients with SLE GN. For example, in the patients assigned to CNI, proteinuria is significantly reduced by 4 weeks [30] or less [31] of CNI therapy. By contrast, in the patients assigned to azathioprine [31] or IVCY [30], proteinuria is not significantly reduced until 3 months of therapy [30, 31]. The rapid onset of the proteinuria reduction with CNI is consistent with the notion that the proteinuria reduction is hemodynamic in origin, related to ability of CNI to stabilize podocytes [29], or both.
- (2) Proteinuria increases rapidly when the CNI is discontinued in SLE GN. For example, in the largest randomized trial involving CNI versus IVCY in SLE GN, 40% of patients assigned to CNI experienced relapse of nephrotic syndrome within 9 months of stopping the CNI. By contrast, none of the patients assigned to IVCY experienced relapse by 9 months [32]. Similar high rates of early relapse of nephrotic syndrome occur in patients with idiopathic membranous nephropathy treated with CNI (reviewed in [33]). This is consistent with the notion that the proteinuria reduction seen with CNI therapy is primarily related to CNI’s hemodynamic/podocyte effect and, therefore, relatively rapidly reversible. By contrast, IVCY induces durable remissions because the nephritic process itself was controlled (i.e. the glomerular deposits tend to be eradicated [34]).

Table 1. Suggested management regimens for severe SLE GN at initial presentation (or at severe relapse)¹

Induction phase (to induce remission)

Drugs

Cyclophosphamide: POCY (1.0–1.5 mg/kg ideal body weight (IBW)). Maximum dose 150 mg/day for 2–4 months depending on response at 2 months. Recommended maximum lifetime cyclophosphamide dose <36 g (reviewed in [36]).

Prednisone (or equivalent glucocorticoid): week 0–2 (1 mg/kg/day IBW, maximum 80 mg/day, 2 divided doses). In very severe disease this may be preceded by 500–1,000 mg/day methylprednisolone i.v. for 3 days. Week 2–4 (0.6 mg/kg/d); week 4–8 (0.4 mg/kg/day); week 8–10 (30 mg/day); week 10–11 (25 mg/day); week 11–12 (20 mg/day).

Monitoring

Hematology: CBC + differential count + platelet count at baseline and each week for 4 weeks. If counts stable and satisfactory can then switch to each 2 weeks for the duration of POCY therapy. If not stable and satisfactory, continue weekly testing. If neutrophil (PMN) decreases to <2,000/mm³ or is decreasing rapidly, decrease POCY dose. For example, if PMN 1,500–2,000, decrease POCY by 50%. If PMN <1,500, hold POCY until PMN >2,000, then restart at ½ previous POCY dose.

Coagulation status: lupus anticoagulant, anti-cardiolipin antibody and D-dimer at baseline. If any result abnormal, assess for thrombotic disorder (reviewed in [37]).

Kidney function: serum creatinine, urinalysis with sediment exam at time of each physician monitoring (see below), and 24-hour urine for creatinine, protein, sodium, urea, potassium (if serum potassium abnormal) at baseline and at 4, 8, and 12 weeks during induction phase. Assess proteinuria from protein/creatinine (P/C) ratio of the intended 24-hour urine. Assess diet compliance from urine Na, K, and urea (discussed in [38]).

Immune status: serum C3 and C4 and quantitative immunoglobulins at baseline and monthly for 2 months. C3 and C4 should increase with each testing. IgG should remain at or above normal. To assess risk of relapse, measure C3 each 2 months if C3 not normal by 4 months.

Physician monitoring: recommended: week 1, 2, 4, 8, 12 for uncomplicated course. Include comprehensive metabolic profile at baseline, and monthly, when needed.

Maintenance phase (to maintain remission)

Drugs

Azathioprine 1.5–2.0 mg/kg IBW (maximum 150 mg/day) OR Mycophenolate mofetil (MMF) (maximum 1,000 mg twice daily). Usual dose 1,500–2,000 mg in divided doses. If low serum albumin, higher dose MMF is appropriate (discussed in [39]). Consider cyclosporin if patient intolerant to azathioprine or MMF.

Prednisone: week 12–13 (17.5 mg/day); week 13–14 (15 mg/day); week 14–15 (12.5 mg/day); week 15–16 (10 mg/day); week 16 and thereafter (IBW <70 kg: 7.5 mg/day; IBW >70 kg: 10 mg/day).

Optimum duration of immunosuppressive therapy has not been rigorously studied. Experience suggests that maintenance immunosuppression should be maintained for at least 1 year after complete remission is achieved. Tapering of immunosuppression can then begin. More than 5 years of immunosuppressive therapy is needed in most of those who experience severe SLE GN (reviewed in [26]). More than 10 years of immunosuppressive therapy is common in many of these patients (reviewed in [26]).

Monitoring

Laboratory: CBC + differential count + platelet count, comprehensive metabolic profile, C3, 24-hour urine for protein, creatinine, urea, sodium, urinalysis. Complete remission is P/C ratio <0.3. C3 should return to normal. Microscopic hematuria may be present for a year or more. The most reliable measure of successful therapy is remission of proteinuria.

Physician monitoring: usually each 2 months. Emphasis on kidney and CV protective therapy.

Adjunctive therapy (to be started at baseline)

Kidney and cardiovascular protective therapy: blood pressure and diet control; ACE inhibitor/ARB therapy, statin/fibrate (discussed in [23, 35]), hydroxychloroquine for anti-inflammatory and antithrombotic effects.¹

Gonadal protection: women: leuprolide 3.75 mg i.m. every 4–6 weeks for the duration of cyclophosphamide therapy; men: testosterone 100 mg i.m. every 2 weeks for the duration of cyclophosphamide therapy. Leuprolide and testosterone should be started about 1–2 weeks before exposure to cyclophosphamide. Initially, these hormones stimulate the ovaries and testes, making them more vulnerable to the effects of the alkylating agent. In situations where delay of cyclophosphamide is not advisable we suggest giving the initial dose of cyclophosphamide i.v., and beginning hormonal therapy 3 days later. By this time 15 cyclophosphamide half-lives will have elapsed. If the patient is to receive oral cyclophosphamide it can be started 3–4 weeks after the initial dose of intravenous cyclophosphamide was administered.¹

¹ For further detail, please refer to Rovin and Stillman [36].

(3) Documentation that CNI therapy reduces proteinuria without eradicating glomerular immune deposits is provided by re-biopsy study in patients with idiopathic membranous nephropathy treated one year or more with cyclosporine. These patients experienced reductions in proteinuria; however, re-biopsy showed that the glomerular accumulation of immune deposits had not decreased. Indeed, generally the deposits were increased [29]. Nevertheless, we suggest that chronic CNI in low dose may have a role in maintenance therapy of SLE GN as reported by Moroni et al. [22, 31].

What Is the Optimal POCY Regimen?

For SLE, we recommend a POCY regimen that is low dose (1.0–1.5 mg/kg ideal body weight) and short course (2–4 months depending upon patient response by 2 months of therapy), concomitant prednisone therapy, and measures for gonadal and bladder protection [21]. We also recommend measures that are kidney and cardiovascular protective [23, 35]. With these approaches, we have

consistently achieved remission rates comparable to IVCY or MMF, and with a side effect profile equivalent to MMF [21]. Importantly, the only patients who progressed to ESRD were the few who were blatantly non-compliant with their drug regimen. Also, we found that African-Americans responded as well to POCY as European-Americans [21]. The recent major clinical trials found that African-Americans responded less well to IVCY than to MMF (reviewed in [21]). This suggests that in African-Americans, POCY is superior to IVCY. The details of our recommended regimen for severe SLE GN are provided in table 1.

In summary, the POCY regimen deserves to compete head-to-head with other immunosuppressive regimens to identify the best available immunosuppressant for SLE nephritis, and ANCA-related vasculitis.

Acknowledgements

Supported in part by NIH grants PO1 DK55546, UL1RR 025755, and 5UO1 DK48621 and the Casto Research Fund.

References

- Dooley MA, Hogan S, Jennette C, Falk R: Cyclophosphamide therapy for lupus nephritis: poor renal survival in black Americans: Glomerular Disease Collaborative Network. *Kidney Int* 1997;51:1188–1195.
- Contreras G, Pardo V, Cely C, et al: Factors associated with poor outcomes in patients with lupus nephritis. *Lupus* 2005;14:890–895.
- Korbet SM, Schwartz MM, Evans J, Lewis EJ: Severe lupus nephritis: racial differences in presentation and outcome. *J Am Soc Nephrol* 2007;18:244–254.
- Appel GB, Contreras G, Dooley MA, Ginzler EM, Isenberg D, Jayne D, Li LS, Mysler E, Sanchez-Guerrero J, Solomons N, Wofsy D: Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. *J Am Soc Nephrol* 2009;20:1103–1112.
- Iglehart JK: Prioritizing comparative-effectiveness research – IOM recommendations. *N Engl J Med* 2009;361:325–328.
- Karim Y, D’Cruz DP: The NIH pulse cyclophosphamide regime: the end of an era? *Lupus* 2004;13:1–3.
- Beck LH Jr, Salant DJ: Treatment of membranous lupus nephritis: where are we now? *J Am Soc Nephrol* 2009;20:690–691.
- Mak A, Cheak AA, Tan JY, Su HC, Ho RC, Lau CS: Mycophenolate mofetil is as efficacious as, but safer than, cyclophosphamide in the treatment of proliferative lupus nephritis: a meta-analysis and meta-regression. *Rheumatology (Oxford)* 2009;48:944–952.
- de Groot K, Harper L, Jayne DR, Flores Suarez LF, Gregorini G, Gross WL, Luqmani R, Pusey CD, Rasmussen N, Sinico RA, Tesar V, Vanhille P, Westman K, Savage CO: Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. *Ann Intern Med* 2009;150:670–680.
- Hebert LA, Rovin BH: Pulse versus daily oral cyclophosphamide in antineutrophil cytoplasmic antibody-associated vasculitis. *Ann Intern Med* 2010;152:64, author reply p 65.
- Petri M: Cyclophosphamide: new approaches for systemic lupus erythematosus. *Lupus* 2004;13:366–371.
- Bargman JM: How did cyclophosphamide become the drug of choice for lupus nephritis? *Nephrol Dial Transplant* 2009;24:381–384.
- Yee CS, Gordon C, Dostal C: EULAR, randomized controlled trial of pulse cyclophosphamide and methylprednisolone versus continuous cyclophosphamide and prednisolone followed by azathioprine and prednisolone in lupus nephritis. *Ann Rheum Dis* 2003;63:525–529.
- Austin HA 3rd, Klippel JH, Balow JE, le Riche NG, Steinberg AD, Plotz PH, Decker JL: Therapy of lupus nephritis: controlled trial of prednisone and cytotoxic drugs. *N Engl J Med* 1986;314:614–619.
- Steinberg AD, Steinberg SC: Long-term preservation of renal function in patients with lupus nephritis receiving treatment that includes cyclophosphamide versus those treated with prednisone only. *Arthritis Rheum* 1991;34:945–950.
- Boumpas DT, Austin HA 3rd, Vaughn EM, Klippel JH, Steinberg AD, Yarboro CH, Balow JE: Controlled trial of pulse methylprednisolone versus two regimens of pulse cyclophosphamide in severe lupus nephritis. *Lancet* 1992;340:741–745.

- 17 Gourley MF, Austin HA 3rd, Scott D, Yarboro CH, Vaughan EM, Muir J, Boumpas DT, Klippel JH, Balow JE, Steinberg AD: Methylprednisolone and cyclophosphamide, alone or in combination, in patients with lupus nephritis: a randomized, controlled trial. *Ann Intern Med* 1996;125:549–557.
- 18 Illei GG, Austin HA, Crane M, Collins L, Gourley MF, Yarboro CH, Vaughan EM, Kuroiwa T, Danning CL, Steinberg AD, Klippel JH, Balow JE, Boumpas DT: Combination therapy with pulse cyclophosphamide plus pulse methylprednisolone improves long-term renal outcome without adding toxicity in patients with lupus nephritis. *Ann Intern Med* 2001;135:248–257.
- 19 Steinberg A: Cyclophosphamide; in Austin KF, Rosen FS, Strom TB (eds): *Therapeutic Immunology*. Oxford, Blackwell Science, 2001, pp 31–50.
- 20 Williams W, Bhagwandass A, Sargeant LA, Shah D: Severity of systemic lupus erythematosus with diffuse proliferative glomerulonephritis and the ineffectiveness of standard pulse intravenous cyclophosphamide therapy in Jamaican patients. *Lupus* 2003;12:640–645.
- 21 McKinley A, Park E, Spetie D, Hackshaw KV, Nagaraja S, Hebert LA, Rovin BH: Oral cyclophosphamide in the management of severe lupus glomerulonephritis: an underutilized therapeutic option. *Clin J Am Soc Nephrol* 2009;4:1754–1760.
- 22 Moroni G, Doria A, Ponticelli C: Cyclosporine (CsA) in lupus nephritis: assessing the evidence. *Nephrol Dial Transplant* 2009;24:15–20.
- 23 Agarwal A, Haddad N, Hebert LA: Progression of kidney disease: diagnosis and management; in Molony D, Craig J (eds): *Evidence-Based Nephrology*. Hoboken, Wiley, 2008, pp 311–322.
- 24 Branten AJ, Vervoort G, Wetzels JF: Serum creatinine is a poor marker of GFR in nephrotic syndrome. *Nephrol Dial Transplant* 2005;20:707–711.
- 25 Mok CC, Lai KN: Mycophenolate mofetil in lupus glomerulonephritis. *Am J Kidney Dis* 2002;40:447–457.
- 26 Houssiau FA, Vasconcelos C, D’Cruz D, et al: The 10-year follow-up data of the Euro-Lupus Nephritis Trial comparing low-dose and high-dose intravenous cyclophosphamide. *Ann Rheum Dis* 69:61–64.
- 27 Rovin BH: Lupus nephritis treatment: are we beyond cyclophosphamide? *Nat Rev Nephrol* 2009;5:492.
- 28 Faul C, Donnelly M, Merscher-Gomez S, Chang YH, Franz S, Delfgaauw J, Chang JM, Choi HY, Campbell KN, Kim K, Reiser J, Mundel P: The actin cytoskeleton of kidney podocytes is a direct target of the antiproteinuric effect of cyclosporine A. *Nat Med* 2008;14:931–938.
- 29 Ambalavanan S, Fauvel JP, Sibley RK, Myers BD: Mechanism of the antiproteinuric effect of cyclosporine in membranous nephropathy. *J Am Soc Nephrol* 1996;7:290–298.
- 30 Bao H, Liu ZH, Xie HL, Hu WX, Zhang HT, Li LS: Successful treatment of class V+IV lupus nephritis with multitarget therapy. *J Am Soc Nephrol* 2008;19:2001–2010.
- 31 Moroni G, Doria A, Mosca M, Alberighi OD, Ferraccioli G, Todesco S, Manno C, Altieri P, Ferrara R, Greco S, Ponticelli C: A randomized pilot trial comparing cyclosporine and azathioprine for maintenance therapy in diffuse lupus nephritis over four years. *Clin J Am Soc Nephrol* 2006;1:925–932.
- 32 Austin HA 3rd, Illei GG, Braun MJ, Balow JE: Randomized, controlled trial of prednisone, cyclophosphamide, and cyclosporine in lupus membranous nephropathy. *J Am Soc Nephrol* 2009;20:901–911.
- 33 Praga M: Response to ‘tacrolimus in membranous nephropathy’. *Kidney Int* 2008;74:824.
- 34 Grootsholten C, Bajema IM, Florquin S, Steenbergen EJ, Peutz-Kootstra CJ, Goldschmeding R, Bijl M, Hagen EC, Van Houwelingen HC, Derksen RH, Berden JH: Treatment with cyclophosphamide delays the progression of chronic lesions more effectively than does treatment with azathioprine plus methylprednisolone in patients with proliferative lupus nephritis. *Arthritis Rheum* 2007;56:924–937.
- 35 Brown C, Haddad N, Hebert LA: Retarding progression of kidney disease; in Johnson R, Fehally J (eds): *Comprehensive Clinical Nephrology*, ed 4. Philadelphia, Elsevier, 2010.
- 36 Rovin BH, Stillman I: The kidney in systemic lupus erythematosus; in Lahita RG, Koike T, Buyon J, Tsokos G (eds): *Systemic Lupus Erythematosus*, ed 5. In press.
- 37 Wu H, Birmingham DJ, Rovin B, Hackshaw KV, Haddad N, Haden D, Yu CY, Hebert LA: D-dimer level and the risk for thrombosis in systemic lupus erythematosus. *Clin J Am Soc Nephrol* 2008;3:1628–1636.
- 38 Hebert LA, Birmingham DJ, Shidham G, Rovin B, Nagaraja HN, Yu CY: Random Spot urine protein/creatinine ratio is unreliable for estimating 24 h proteinuria in individual SLE nephritis patients. *Nephron Clin Pract* 2009;113:177–182.
- 39 van Hest RM, Mathot RA, Pescovitz MD, Gordon R, Mamelok RD, van Gelder T: Explaining variability in mycophenolic acid exposure to optimize mycophenolate mofetil dosing: a population pharmacokinetic meta-analysis of mycophenolic acid in renal transplant recipients. *J Am Soc Nephrol* 2006;17:871–880.

Editorial Comment

R.J. Glassock, Laguna Niguel, Calif.

Mark Twain once said ‘*the reports of my death have been greatly exaggerated*’. This famous quotation might also be applied to the report of Hebert and co-workers on the looming extinction of the use of oral cyclophosphamide in the treatment of severe lupus nephritis and other auto-immune diseases involving the kidneys. Actually, the application of short-term oral cyclophosphamide in the management of severe lupus nephritis is very much alive (although not necessarily thriving), at least in

Columbus, Ohio; Chicago, Ill., and in many parts of the UK, Australasia and Europe. In my own practice, I have only used intravenous cyclophosphamide on one occasion in the past four decades. Hebert and friends bring to our attention, in a most forceful way, how weak the evidence is for superiority in both efficacy and safety of an intravenous cyclophosphamide regimen compared to a low-dose, short-term oral cyclophosphamide regimen in management of severe auto-immune renal disease. In

part, this is due to the paucity of head-to-head comparisons of efficacy in randomized clinical trials and the lack of clear-cut answers to the issue of comparative toxicity of the two regimens when cases are stratified according to a priori risk of treatment-induced complications. Lower cumulative dosage of cyclophosphamide in IV-based compared to oral-based regimens needs to be considered in the context of overall efficacy (remission, relapses, avoidance of ESRD), especially with long-term, follow-up, and the cumulative occurrence of adverse events (the burden of toxicity). Claims of preferential benefits of one

regimen over the other in specific ancestral groups identified in post hoc analyses need to be confirmed in prospective randomized studies. The overall cost-effectiveness of measures to avoid bladder and gonad toxicity in either oral or IV-based regimens deserve careful scrutiny and testing. Nevertheless, the provocative essay by Hebert and colleagues should cause nephrologists to pause and ponder on how 'gold standard' therapies evolve and not rush to judgment in relegating reasonable treatment strategies to the 'trash bin' of history. Rather, *'He who refuses to learn deserves extinction'* (Rabbi Hillel).