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COMMENTARY

Crossing the Atlantic: The Euro-Lupus Nephritis Regimen in North America

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More than a quarter century has passed since a landmark trial at the National Institutes of Health (NIH) established pulse intravenous (IV) cyclophosphamide (CYC) and high-dose glucocorticoids as the standard of care for active lupus nephritis (1). In the ensuing years, numerous other conventional and biologic therapies have been proposed and tested, most notably mycophenolate mofetil (MMF) (2) and rituximab (3), but none has been demonstrated to be superior to IV CYC during induction treatment of active disease.

Until the emergence of new treatment strategies that are proven to be superior to IV CYC, there will be a need for evidence-based best practices to guide the use of CYC. For this reason, the Euro-Lupus Nephritis Trial (ELNT) compared 2 approaches to IV CYC therapy. One approach consisted of 44 weeks of IV CYC based on the NIH regimen, followed by maintenance therapy with azathioprine (AZA). The other approach consisted of just 6 biweekly infusions of IV CYC at lower doses (500 mg/infusion), followed by maintenance therapy with AZA (4,5). After 10 years of followup, efficacy was comparable in the 2 groups; the frequency of serious infectious complications was lower in the low-dose IV CYC group, but this advantage did not reach statistical significance. Despite the ELNT results, many lupus experts have been hesitant to adopt the modified regimen, citing concerns that the findings in a population of northern European, primarily Caucasian, subjects might not be generalizable to other populations that tend to have more severe and refractory nephritis (e.g., black and Hispanic patients).

A recent trial of abatacept for lupus nephritis (NCT00774852) has provided new data that may allay concerns about the generalizability of the ELNT regimen (6). The Abatacept and Cyclophosphamide Combination: Efficacy and Safety Study (ACCESS) trial, in which all subjects received the ELNT regimen as background therapy, was conducted in a North American patient population that was 37% black and 41% Hispanic. Although the trial did not demonstrate a benefit of abatacept, the results were striking in that the rate of complete response in both treatment groups (with or without abatacept) was >30% at 6 months, which is higher than rates of complete response in other recent lupus nephritis trials (2,3). The high response rate was particularly surprising given the racial and ethnic diversity within the study population.

We are keenly aware that it is hazardous to compare results from trials with different study designs and populations. Among other potential pitfalls, the studies do not all use the same criteria to define complete response. To address this problem, we applied the same response criteria to the raw data from the ELNT, the ACCESS trial, and the Aspreva Lupus Management Study (ALMS) (NCT00377637) (Table 1). To enable the use of data elements that were available from all 3 trials, we defined complete response at 6 months as proteinuria ≤0.5 gm/24 hours and no worsening of the serum creatinine level relative to baseline.

According to this analysis, the rate of complete response was strikingly similar among all of the groups. The MMF standard-of-care regimen yielded a complete response rate of 21% in the ALMS trial. The high-dose IV CYC regimen yielded a complete response rate of 22% and 24% in the ALMS and ELNT trials, respectively, and the low-dose IV CYC regimen yielded a complete response rate of 23% and 25% in the ACCESS

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Table 1. Rates of complete response in the ELNT, the ACCESS trial, and the ALMS, determined using the same response criteria*

Treatment regimen	% with proteinuria >3 gm/24 hours at baseline†	Complete response rate (%) at 6 months‡
ELNT–low dose (n = 36)	42	25
ELNT–high dose (n = 38)	45	24
ACCESS (n = 66)	52	23
ALMS–MMF (n = 169)	57	21
ALMS–CYC (n = 171)	60	22

* ELNT = Euro-Lupus Nephritis Trial; ACCESS = Abatacept and Cyclophosphamide Combination: Efficacy and Safety Study; ALMS = Aspreva Lupus Management Study; MMF = mycophenolate mofetil; CYC = cyclophosphamide.
† All subjects with proteinuria >1 gm/24 hours at baseline were included in the analysis.
‡ Complete response was defined as proteinuria ≤0.5 gm/24 hours and no worsening of the serum creatinine level, i.e., no more than 0.2 mg/dl increase from baseline.

and ELNT trials, respectively. This analysis does not resolve other potential pitfalls relating to differences between study populations. For example, the study populations in the 3 trials varied somewhat with respect to the severity of lupus nephritis, as reflected by the frequency of nephrotic levels of proteinuria at baseline (Table 1). Nonetheless, the results are intriguing in that they suggest that the efficacy of the ELNT regimen may be comparable to that of standard-of-care regimens consisting of high-dose IV CYC or MMF, even among the racially and ethnically diverse population in the ACCESS trial. While these findings do not definitively establish that results obtained with the ELNT regimen are comparable to those of current standard-of-care regimens, they provide an evidence-based rationale for reconsidering the doubts that have heretofore made some clinicians reluctant to prescribe the low-dose IV CYC regimen.

How might we explain the surprising observation that a therapeutic regimen with less exposure to cyclophosphamide might have the same efficacy as a regimen with much greater exposure? Perhaps 6 months is not long enough to detect differences among the regimens, although the data on that time point from the 5- and 10-year followup of the ELNT trial suggest otherwise (4,5). Alternatively, when a comparison of several immunosuppressive induction regimens fails to identify any one that is superior to the others, we must consider the heretical possibility that none of the immunosuppressive drugs adds benefit to glucocorticoids alone during the early stages of induction therapy. In this regard it is noteworthy that each of the trials compared in Table 1 rested on a foundation of glucocorticoid use. The ELNT trial began with 3 daily IV pulses of methylprednisolone (750 mg/day) followed by oral glucocorticoid therapy at an initial dosage of 0.5–1.0 mg/kg/day depending on the severity of the renal disease. After 4 weeks at the initial dosage, the glucocorticoid was tapered by 2.5 mg every 2 weeks to an eventual maintenance dosage of 5.0–7.5 mg/day (4). In both the ALMS trial (2) and the ACCESS trial (6), prednisone was begun at 60 mg/day and then tapered gradually to a maintenance dosage of 10 mg/day.

Finally, in mice, depletion of B cells by cyclophosphamide is followed by emergence of autoreactive B cells during reconstitution of the B cell repertoire (7). In humans, B cell depletion promotes high levels of BAFF (8), and high levels of BAFF promote reconstitution of the B cell compartment with a repertoire that is skewed toward autoreactivity (9,10). Thus, the high-dose regimen may result in a continuous need for cyclophosphamide to delete newly generated autoreactive B cells, whereas the low-dose regimen with its early switch to AZA may have less impact on BAFF levels and might therefore be less likely to promote reemergence of autoreactive B cells. While this is at present only a speculation, it does raise the question of whether we may have adopted an approach to the use of cyclophosphamide in which more aggressive treatment may actually have undermined the therapeutic goal and led to the requirement for continued cyclophosphamide exposure. Based on available evidence, and the principle of first doing no harm, the ELNT regimen should be considered an option for all patients with lupus nephritis.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Wofsy had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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