2015

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HHS Public Access

Author manuscript

Arthritis Rheumatol. Author manuscript; available in PMC 2016 May 01.

Published in final edited form as:

Arthritis Rheumatol. 2015 May ; 67(5): 1144–1146. doi:10.1002/art.39067.

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 cyclophosphamide (IVC) 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 IVC during induction treatment of active disease.

Until new therapeutic strategies emerge that are proven superior to IVC, there will be a need for evidence-based best practices to guide the use of cyclophosphamide. For this reason, the Euro-Lupus Nephritis Trial (ELNT) compared two approaches to IVC treatment. One approach consisted of 44 weeks of IVC based on the NIH regimen, followed by maintenance therapy with azathioprine (AZA). The other approach consisted of just six biweekly infusions of IVC at lower doses (500 mg/infusion), followed by maintenance therapy with AZA (4,5). After 10 years of follow-up, efficacy was comparable in the two groups; the frequency of serious infectious complications was lower in the low-dose IVC 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 ACCESS trial, in which all subjects received the ELNT regimen as background therapy, was conducted in a North American study population that was 37% Black and 41% Hispanic. Although the trial did not demonstrate a benefit for abatacept, the result was striking in that the complete response (CR) rate in both treatment groups (with or without abatacept) was >30% at six months, which is higher than CR rates in other recent lupus nephritis trials (2,3). The high

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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 different study 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 ELNT, ACCESS, and the Aspreva Lupus Management Study (ALMS) (NCT00377637) (Table 1). In order to use data elements that were available from all three trials, we defined CR at 6 months as proteinuria <500 mg/24 hours and no deterioration in serum creatinine relative to baseline. According to this analysis, the CR rates in all of the groups were strikingly similar. The MMF standard-of-care regimen produced a CR rate of 21% in the ALMS trial. The high-dose IVC regimen produced a CR rate of 22% and 24% in the ALMS and ELNT trials, respectively. The low-dose IVC regimen produced a response rate of 23% and 25% in the ACCESS 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 three 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 the sense that they suggest that the ELNT regimen may be comparable to standard-of-care regimens consisting of high-dose IVC or MMF, even among the racially and ethnically diverse population in the ACCESS trial. While these findings do not definitively establish that the ELNT regimen is comparable to current standard-of-care regimens, they provide an evidence-based rationale for reconsidering the doubts that have heretofore made some clinicians reluctant to employ the low-dose IVC 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 six months is not long enough to detect differences among the regimens, although the data on that point from the 5- and 10-year follow-up 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 corticosteroids 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 three daily intravenous pulses of methylprednisolone (750 mg/day) followed by oral glucocorticoid therapy at an initial dose of 0.5 – 1.0 mg/kg/d depending on the severity of renal disease. After four weeks at the initial dose, the glucocorticoid dose was tapered by 2.5 mg every two weeks to an eventual maintenance dose of 5.0 – 7.5 mg/d (4). In both the ALMS (2) and ACCESS (6) trials, prednisone was begun at 60 mg/d and then tapered gradually to a maintenance dose of 10 mg/d.

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 B-cell activating factor (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 a therapeutic approach to the use of cyclophosphamide in which more aggressive treatment may actually have undermined the therapeutic goal and have 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 lupus nephritis patients.

Acknowledgments

The authors are grateful to the Immune Tolerance Network for supporting the ACCESS trial (NIH contract N01-AI-15416; protocol number ITN034AI) and to Vifor Pharmaceuticals (formerly Aspreva) for sharing data from the Aspreva Lupus Management Study (ALMS) for inclusion in Table 1.

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Table 1

Complete response rates in the Euro-Lupus Nephritis Trial (ELNT), the ACCESS Trial, and the Aspreva Lupus Management Study (ALMS), using the same response criteria. Analysis of study subjects with proteinuria >1 gm/24 hours at baseline.

	Proteinuria at Baseline* (>3 gm/24 hr)	Complete Response Rate† (at 6 mos)
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-CTX (N=171)	60%	22%

*Percent of subjects with proteinuria >3 gm/24 hours at baseline. [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 deterioration in serum creatinine (defined as no more than 0.2 mg/dL increase compared to baseline)