Mycophenolate or Cyclophosphamide in Lupus Nephritis: Which One to Use in Indian Patients?

Renal involvement in the form of lupus nephritis (LN) remains a major challenge for treatment in patients with systemic lupus erythematosus.[1] Out of the various classes of LN, the proliferative LN (Class III and IV) not only are more common in India but also are more severe and thus require more aggressive therapy.[2] A delayed initiation of therapy or a poor response to the initial immunosuppressive therapy predicts poor long-term outcome and more progression to end-stage renal disease in proliferative LN. Thus, it is important to treat the proliferative LN early and adequately.[1]

Till date, two forms of induction therapies are commonly used: intravenous (IV) cyclophosphamide (IV-CYC) or oral mycophenolate mofetil (MMF). IV-CYC can further be given in two different regimens: high dose National Institute of Health regimen (NIH)[3] or a low-dose Euro-LN trial regimen (ELNT).[4] Although there are trials comparing IV-CYC and MMF from West, good quality data are lacking from India. The data from West suggests that oral MMF is preferable in African-Americans while ELNT may be preferable in Caucasians.[5] Most of the data from India are in the form of observational studies and suggest a comparable rate of response with either IV-CYC or oral MMF.[6,7] We published a randomized trial comparing ELNT regimen with oral MMF in patients with less severe proliferative LN and observed a comparable rates of treatment response in the two arms.[8]

In the recent past issue of the Indian Journal of Nephrology, Sahay *et al*. have published an article "Mycophenolate versus CYC for LN."[9] In this study, the authors have compared the three different induction regimens, i.e., NIH, ELNT, and oral MMF in patients with proliferative LN (Class III, IV, III + V, and IV + V). The authors studied 144 patients of proliferative LN, of which about 12.5% were crescentic LN, and 14.6% were dialysis requiring. The patients were randomly allocated to receive one of the three induction regimens and the treatment response at the end of 6 months was compared. Although the baseline characteristics were similar in the three groups; patients receiving MMF were much younger as compared to the CYC group. This may indicate a bias in allocation, where younger patients might have been preferably given MMF. All the three treatment regimens also consisted of three pulses of injection methylprednisolone (500 mg/m^2 each) followed by oral steroids 1 mg/kg/day, which was tapered to 10 mg/day by 3 months and continued thereafter. The dose of MMF was 1200 mg/m^2, which was used upfront without any uptitration. The dose of MMF did not exceed 2.0 g/day with a mean dose of 1.8 g/day.

The authors noted a comparable response rate in the three groups (NIH-71.4%, ELNT-65%, and MMF-72.9%), including in those patients with renal failure. However, whether the response rates were similar in those who were dialysis requiring at presentation is not clear.

The main worrisome part of the study is the side effect profile in the different treatment arms.[9] Amenorrhea was significantly more in patients receiving IV-CYC. Although in the text, authors mentioned equal rates of amenorrhea in patients receiving NIH and ELNT regimens, the figures are different in Table 3, where amenorrhea is less common in patients receiving ELNT. Another side effect which is not easily explainable is high incidence of diarrhea in patients receiving IV-CYC. Diarrhea is a known side effect with MMF; however, a similar proportion of patients receiving IV-CYC developed diarrhea in this study.[9] Whether this is an infective complication or not is not clear. Steroid-related toxicities were also very high in the study. This included certain side effects which are seen only with long-term steroid use and are unlikely to develop within 6 months, such as cataract and avascular necrosis. This may be due to either a high dose of steroids used in these patients, as the dose was not decreased below 10 mg/day or the patients might have been receiving steroids in the past before being enrolled in the study. A total of 5 patients died, all of whom received IV-CYC as induction therapy. Of these, three died due to extrarenal manifestations of disease. This may again indicate a bias in prescribing the IV-CYC to those with severe extrarenal manifestations. Two patients receiving IV-CYC died of severe sepsis though the overall infection rates were similar in the three groups.

The kind of side effect profile observed in the present study may preclude the use of IV-CYC in these patients.[9] However, such a difference in side effect profile was not seen in another studies performed in India[7,8] or from West.[4,10] In our study, we observed equal number of infection episodes and menstrual abnormalities in patients receiving either MMF or IV-CYC; however, patients receiving MMF experienced more gastrointestinal (GI) symptoms.[8] Although the ELNT trial did not provide details regarding GI side effects in the low-dose CYC group, no one withdrew from the study due to GI toxicity.[4] Similarly, the rates and severity of infections were equal in the two groups.[4] The aspreva lupus management study also reported similar rates of overall side effects, infections, and menstrual abnormalities in the groups receiving either high dose IV-CYC or oral MMF.[10] It is important to note that the cost of treatment is markedly lower in patients receiving IV-CYC.[8,9] Thus, in a resource-limited setting,

it may be a kind of trade-off for the clinician, to choose between a cheaper alternative with increased incidence of side effects compared to an expensive but relatively less toxic drug. The regimen of low dose CYC in the form of ELNT regimen may be best suitable in such scenario with acceptable side effect profile and low cost.

The limitations mentioned by the authors included smaller sample size, single-center study and short follow-up, which is a fallacy of other Indian studies also.[7,8] It is an opportune time for various Indian centers working in this field to collaborate and come out with good quality multicentric data with long-term follow-up.

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