How did cyclophosphamide become the drug of choice for lupus nephritis?

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Lessons learned from the early studies of corticosteroids and other agents

Thirty years ago, Donadio and colleagues published the results of a randomized study in 50 patients with diffuse proliferative lupus nephritis and reduced creatinine clearance [1]. The patients were randomly assigned to either prednisone alone or prednisone in combination with oral cyclophosphamide (CTX). The corticosteroid-only group received 60 mg daily for 1 to 3 months, and then tapered to receive 20 mg daily by 6 months. Those in the second group received, in addition, oral CTX 2 mg/kg body weight, which was subsequently titrated to the peripheral white cell count. The majority of patients in both groups improved with therapy. The patients who quickly progressed to ESRD were equally divided between the two treatment regimens. It was in the long-term follow-up that the CTX group appeared to do better: after a mean of 43 months, 10 of 21 patients in the prednisone-only group relapsed, compared to 3 of 21 in the prednisone-CTX group. Despite the difference in flare rates, though, the proportion of the patients alive with stable or even improved renal function was similar with the two treatment regimens. The stated key point from this study was that patients on combined treatment were less likely to flare compared to those receiving only prednisone. However, several other important observations were made:

1. Patients in both groups were equally likely to improve over the first 6 months. This is an important lesson for treating an acutely ill lupus patient. Some physicians feel that there is an urgency to deliver intense immunosuppressive therapy in the first few days of treatment of lupus nephritis. This can lead to serious infectious consequences. In addition, the administration of pulse intravenous CTX, even in reduced doses, can lead to an unpredictable nadir in white blood cell count, especially in patients with impaired renal function. The development of marked leucopaenia puts the patient at risk for severe infection. This study suggests that the most important drug to give at the outset is high-dose corticosteroid, which is in keeping with the fact that the immunosuppressive effects of CTX are not immediate. The decision about other agents is more relevant for the longer term management of the patient, in order to be able to reduce the dose of corticosteroids and to prevent relapse, and can be made in the days to weeks that follow the presentation.

2. The early treatment failures were in patients with advanced glomerulonephritis and severely impaired renal function. Edmund Lewis, in a trenchant editorial on the management of lupus, quoted Galen as saying ‘All who drink of this remedy recover in a short time except those whom it does not help, who all die. Therefore it is obvious that it fails only in incurable cases’ [2]. In other words, mostly any treatment works in mild disease, and almost none in severe disease. The same philosophy applies to disease associated with advanced renal damage. One of the philosophical divides between nephrologists and rheumatologists is the chance of effecting an improvement in kidney function in the face of chronic advanced disease [3]. While there is always the concern about a sampling artefact from a renal biopsy, certainly the presence of extensive tubulointerstitial fibrosis and glomerular atrophy, especially in a patient known to have chronically elevated creatinine, bodes poorly for any chance of renal recovery. Therefore, the risk of immunosuppression to save dying kidneys must be weighed against the chance of benefit.

In 1984 a pooled analysis of eight studies of lupus nephritis, comprising 250 patients (including children), 198 renal biopsies and 167 patients with biopsy evidence of diffuse proliferative lupus nephritis, was published in The New England Journal of Medicine [4]. Three of the studies came from the National Institutes of Health (NIH), and the study by Donadio discussed above was also included. Of the 250 patients, 113 received only corticosteroids, and the rest received corticosteroid and other immunosuppressive agents
(azathioprine and CTX). Patients receiving the corticosteroid and another agent had a lower rate of deterioration of kidney function. In addition, the prednisone-only patients were twice as likely to reach ESRD and to die compared to the other group. When the immunosuppressive drug was subdivided by drug received, there were only approximately 60 patients in each group (pred versus CTX/pred; pred versus AZA/pred), and statistical significance was lost for most comparisons, although subjects treated with azathioprine and prednisone still showed statistically less renal deterioration compared to those receiving prednisone alone [4]. Furthermore, there was a decrease in the total deaths in the azathioprine group, but not in the CTX group when each was compared with the prednisone-only cohort. Indeed, the addition of CTX (but not azathioprine) was associated with a slightly higher death rate from non-renal causes. None of these studies was a head-to-head comparison of the two immunosuppressive agents. However, the pooled analysis added credence to Donadio’s finding that prednisone in combination with another immunosuppressive drug was more efficacious than prednisone alone. Within the limitations of this kind of analysis, azathioprine appeared to be a helpful drug in the management of diffuse proliferative lupus nephritis without the risk of increasing non-renal (?infective) deaths, as was suggested with CTX. The latter part of the 1980s was dominated by a series of publications from the National Institutes of Health on the interim and final outcomes of different treatment protocols for the treatment of lupus nephritis [5–8]. Crossovers in therapy were allowed, and in 1979 the protocol was modified so that the immunosuppressive drugs could be discontinued [8]. Nevertheless, the report at 7 years could find no difference in renal deterioration between the patients taking CTX versus those on azathioprine. However, again there is a hint of the price to be paid with CTX that was first suggested in Felson’s analysis [4]. Of the 20 azathioprine-treated patients, 3 discontinued therapy because of infection or cancer, whereas of the 18 CTX-treated patients 3 patients developed severe infection, 3 haemorrhagic cystitis and 3 cancer. Two patients receiving azathioprine developed herpes zoster compared to six with CTX [8]. Another follow-up report just 1 year later, focusing on histologic predictors of outcome, was published in The New England Journal of Medicine in 1984 and did not find a difference among the different cytotoxic-drug regimens and renal outcome [9].

The NIH Publication and the popularization of pulse CTX

Everything changed with the publication of another progress report, again in The New England Journal of Medicine, in 1986 [10]. Patients who entered the lupus nephritis trials at the NIH between 1969 and 1981 were included. There were 107 patients in total, and they were randomized into one of five treatment protocols: (1) high-dose prednisone (1 mg/kg); (2) azathioprine (up to 4 mg/kg) + low-dose oral prednisone; (3) oral CTX (up to 4 mg/kg) + low-dose oral prednisone; (4) combined oral azathioprine and oral CTX (up to 1 mg/kg of each) and (5) intravenous CTX (0.5–1.0 g/m² every 3 months titrated to a peripheral white cell count nadir) + low-dose oral prednisone. As mentioned, the protocol was changed in 1979 so that immunosuppressive agents could be discontinued. Furthermore, not all therapies were offered contemporaneously. Groups 1, 2 and 3 were enrolled from 1969 to 1976, and groups 4 and 5 from 1973 to 1981. It is also important to note that the median serum creatinine was 1.0 mg/dl (88 μmol/l). There has been criticism of subsequent lupus trials [11,12] that the renal disease in these trials was ‘too mild’. However, the serum creatinine was almost identical in these three studies.

While this was one of the largest cohorts of lupus patients to be examined, the numbers were still quite small. At 120 months of follow-up, where the curves diverge, the number of patients still in the study was 11 in the azathioprine, 8 in the oral CTX and 3 in the combined oral azathioprine/CTX groups. There was just one patient in group 5 (IV CTX).

Despite the sizable methodological weaknesses outlined above, the ‘NIH protocol’ of intravenous pulsed CTX became widely accepted as the gold standard of treatment. It was new therapy, carried the cachet of the National Institutes of Health and was the protocol to which all others were compared thereafter. Furthermore, as Lewis observed: ‘The tendency to recommend parenteral cyclophosphamide may in part reflect the mystique associated with a more invasive intervention’ [2]. Finally, despite evidence that started to accrue suggesting that this therapy may not necessarily lead to superior results compared to other immunosuppressive regimens, it continued to be defended by the original investigators [13].

The paper by Contreras et al. was a randomized controlled trial of pulse CTX, mycophenolate mofetil (MMF) and azathioprine in the treatment of proliferative lupus nephritis [14]. Unfortunately, the water was muddied by the protocol, in which all groups received induction therapy with up to seven monthly boluses of CTX before being randomized to the three treatment arms. Nonetheless, both azathioprine and MMF-treated subjects fared well in this trial. The cumulative rate of renal survival was 95% in the MMF group, 80% in those receiving azathioprine and 74% in the intravenous CTX. Importantly, of the five patients who died during the trial, four were in the CTX arm and died of sepsis (the fifth death was in a patient receiving MMF). Again, similar to the observations of Felson’s analysis 20 years before, no patient in the azathioprine group died during the study.

Is azathioprine the hydrochlorothiazide of lupus therapy?

Hydrochlorothiazide is an excellent and useful drug for the treatment of essential hypertension, and yet remains perpetually under-used [15]. Potential explanations include its being off-patent, which implies that no pharmaceutical company stands to make a sizable profit over the sale of the drug. Therefore, there will not be a lot of resources
expended to promote the sale of this medication. Relatively, it is inexpensive. While this is a boon to those patients with limited financial resources, it may also relegate this drug to ‘second-class’ status for no reason other than its being so cheap. It may be perceived that the more expensive a drug, the better and more ‘special’ it must be.

Azathioprine may be the hydrochlorothiazide equivalent in the treatment of lupus. Despite the pooled analysis of Felson in which azathioprine appeared to perform even better than daily oral CTX (although none of the studies had a head-to-head comparison) [4], it also became second-class treatment. In a review of the management of lupus nephritis delivered at the annual meeting of the American Society of Nephrology, the speaker referred to the Contreras study as a comparison of CTX and MMF (no mention of the azathioprine arm). At another major nephrology conference that I attended, a clinico-pathological conference concerned a pregnant woman with a flare of lupus nephritis. The discussant mentioned that neither CTX nor MMF could be used because of the risk of teratogenicity, and settled for corticosteroids alone. Azathioprine did not enter the discussion.

The best thing about MMF is that it will convince people that there are therapies for lupus nephritis other than pulse CTX

The issue of induction of therapy was re-addressed by the study of Ginzler and colleagues where patients were randomized to receive MMF versus pulse CTX and was designed as a short-term (24 week) equivalency study [12]. The majority of patients had class IV lupus nephritis, but a sizable proportion had class III or membranous variants. The serum creatinine was \( \sim 1.07 \) mg/dl, which has been criticized as being too ‘good’, but indeed was no different than the median creatinine in the NIH report of 1986 [10]. The number of renal flares in this relatively short follow-up time was identical with the two protocols, but there was more renal failure and twice the number of deaths \((P = \text{NS})\) in the group that received the CTX. The authors concluded that MMF was the more effective drug compared to CTX although the study was designed as a non-inferiority trial. Although azathioprine was mentioned in passing in the discussion, the emphasis was on the utility of MMF for induction of therapy for lupus nephritis. There has never been a head-to-head comparison of AZA with MMF, but certainly in the Contreras study both were associated with better outcomes compared to CTX. In the latter study, there appeared to be a trend to more relapses in the AZA arm compared to the MMF arm, but the number of patients was small and the difference was not statistically significant. However, the high profile of the MMF studies has given credence to the idea that CTX is not the only way to treat severe proliferative lupus nephritis, and perhaps this will open clinicians’ minds to therapy with azathioprine also, especially in those patients who cannot afford it or who are intolerant of MMF. The pregnant patient with lupus presents a special challenge. Azathioprine is a D class drug, acknowledging that there is evidence of human fetal risk, but the benefits from its use may be acceptable in the pregnant patient with active lupus. This is extrapolated from the pregnant transplant patient where this drug is usually not discontinued [16].

Is the problem with CTX itself, or are we using too high a dose?

The studies of the past 30 years have shown a worrisome trend of increased incidence of severe infections and death in patients who received CTX [4,11,12,14].

It would be hoped that the ‘payoff’ for the increased infections and deaths is that the CTX is the more potent immunosuppressive agent and, therefore, leads to a better control of the disease. Unfortunately, the same studies do not strongly support this contention.

The Euro-Lupus Nephritis Trial examined the effects of ‘low-dose’ (3 g) versus ‘high-dose’ (mean of 8.5 g) CTX in a randomized study of 90 patients with lupus nephritis. Severe infections were more common in the high-dose group, although, interestingly, the two deaths occurred in the patients taking low-dose CTX. There was a trend towards more renal remissions in the low-dose group \((P = \text{NS})\), and the number of renal flares was no different [17]. Of the 16 patients who experienced a renal flare in the high-dose group, 7 experienced the flare while being actively treated with the CTX pulses. This interesting trial suggests that the same result can be reached with lower rather than higher doses of CTX and with a lower risk of severe infections.

A different way of looking at this study, aside from the dosing of CTX, was that the low-dose group changed to AZA maintenance after just 12 weeks, whereas the high-dose group continued with the CTX and changed to AZA after ~12 months. Despite the early switch to AZA at Month 3 in the ‘low-dose’ CTX group, there were no more flares compared to the cohort continuing CTX [17]. So this study could also be construed as one comparing changing to AZA at 3 months versus continuing CTX for another 9 months and, once again, azathioprine comes out well.

Conclusions

This editorial is not intended to provide an in-depth review of every study examining immunosuppressive therapy of severe lupus nephritis. It is to highlight some important observations that run as a leitmotif through major studies of the past three decades. High-dose corticosteroids remain the mainstay of therapy for the initial treatment of severe lupus nephritis. A second agent is recommended as it is associated with a lower rate of relapse and, in most cases, better renal outcome. The second drug should be approached as a ‘disease-modifying’ agent and does not necessarily have to be started on the day of diagnosis, especially if there is suspicion of intercurrent infection. The renal prognosis is ultimately determined by the severity of disease and, relatedly, the amount of fixed renal damage. It is clear that the use of potent immunosuppressive agents may effectively treat the lupus, but are themselves associated with worrisome short-term and (perhaps unknown?) long-term side effects. All intensive immunosuppressive therapy can
be associated with severe side effects up to and including death. In this regard, data from the recent ASPREVA Study are awaited with interest. However, it is important to realize that CTX should not be considered the only useful drug in the management of lupus nephritis.

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References


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