Fellows First

Minimization in Minimal Change Disease: Maximal Change in Practice?

By Dearbhla Kelly

Minimal change disease (MCD) is one of the major causes of idiopathic nephrotic syndrome, accounting for up to 70%–90% of cases in children and approximately 15% of cases in adults (1). The characteristic appearance of MCD on a kidney biopsy is normal glomeruli on light microscopy with diffuse effacement of the epithelial foot processes on electron microscopy. The pathogenesis of MCD is not fully elucidated, but systemic T cell dysfunction producing increased levels of a glomerular permeability factor has been implicated (2, 3). Although the pathogenesis remains uncertain, similar to focal segmental glomerulosclerosis, a circulating factor that damages the glomerular capillary wall has been postulated, resulting in proteinuria and foot process fusion (1).

Glucocorticoid therapy has been the mainstay of therapy for MCD for decades. This management strategy in children has been informed by several large prospective randomized clinical trials (RCTs) in addition to observational studies (4). Over 90% of children respond with complete remission to initial steroid therapy (5). The recommendation for glucocorticoid therapy in adults has been informed mostly by observational studies (4), as RCT data are lacking, with the majority of information coming from a single RCT published in 1970. This trial compared low-dose prednisone (<30 mg/day) with no specific therapy among 31 adults. More than 75% of treated patients had remission of proteinuria to less than 1 g/day within 6 months (6). Subsequently, several retrospective observational studies have demonstrated a high but variable response rate (67%–100%) in adult patients treated with higher doses (e.g., 60 mg/day or 1 mg/kg/day) (7–9). Kidney Disease: Improving Global Outcomes (KDIGO) currently recommends glucocorticoid therapy as treatment for the initial episode of adult MCD, while acknowledging that there is only low-quality evidence available and that this recommendation is based largely on extrapolation from trial data in children in addition to small observational studies in adults (10).

Steroids, however, have a significant adverse side effect profile, including Cushingoid features (11), weight gain (12), hypertension (13), gastrointestinal bleeding (14), osteoporosis (15), diabetes (16), and increased infection risk (17). This is particularly concerning because a prolonged course of steroid treatment is often required in MCD, and relapse rates in adults can be high (8). Therefore, there has been increasing interest in steroid-sparing or minimizing regimens. Steroid-sparing regimens have already been investigated for other glomerulonephritides, including antineutrophil cytoplasmic antibody (ANCA) vasculitis (18) and membranous nephropathy (19), with encouraging results to date.

One large investigation into a steroid-sparing regimen for MCD is the Tacrolimus Versus Prednisolone for the Treatment of Minimal Change Disease (MinTac) trial, a multi-center, open-label RCT based in the United Kingdom, in which 52 adult patients with MCD were randomized to treatment with either oral tacrolimus at 0.05 mg/kg twice daily for 12 weeks (then tapered over a further 8 weeks) or prednisolone at 1 mg/kg daily up to 60 mg daily for 16 weeks. The primary objective was to demonstrate the non-inferiority of tacrolimus compared to prednisolone for inducing remission in MCD, in addition to showing that relapse rates were similar, and adverse events were less common. Although there was no statistically significant difference in the primary outcome (complete remission at 8 weeks) between groups (68% for tacrolimus vs. 84% for prednisolone; p = 0.32), the a priori definition of non-inferiority was not met in either the per-protocol or the intention-to-treat analysis. Relapse rates (73% for tacrolimus vs. 74% for prednisolone; p = 0.99) and safety profile were found to be similar between groups (20). This was the first study to investigate the use of tacrolimus monotherapy to treat MCD, and although the sample size was small, and further research is required, the results do suggest that tacrolimus may be an effective alternative treatment to steroids for MCD in adult patients.

More recently, another randomized controlled trial compared combined tacrolimus and low-dose steroid treatment with the standard high-dose steroid protocol in adult patients (21). In this open-label, non-inferiority study, 144 adults with MCD were randomized to receive either 0.05 mg/kg twice-daily tacrolimus plus once-daily 0.5 mg/kg prednisolone or once-daily 1 mg/kg prednisolone alone for up to 8 weeks or until achieving complete remission. The steroid dose was then tapered to a maintenance dose of 5–7.5 mg/day in both groups, 2 weeks after complete remission, until 24 weeks after study-drug initiation. The primary end point, defined as complete remission within 8 weeks (urine protein:creatinine ratio <0.2 g/g), was achieved in 79.1% of those receiving tacrolimus and low-dose steroid compared to 76.8% receiving high-dose steroid, confirming non-inferiority of this treatment protocol. Of note, the relapse rate was also much lower in the combined tacrolimus/low-dose steroid protocol compared to the high-dose steroid-alone group (5.7% vs. 22.6%, respectively; p = 0.01) with no major safety differences observed (21). Studies investigating steroid minimization regimens for MCD are summarized in Table 1. Use of rituximab has already been shown to facilitate such regimens in other glomerulonephritides (18), and there is some emerging evidence from case series to suggest that it also could have a future role in steroid-sparing treatment strategies for MCD (22, 23).

Tacrolimus, with or without low-dose steroids, therefore appears to be an effective alternative to high-dose steroids in MCD, particularly in patients at high risk of adverse effects from steroids, such as those with diabetes, obesity, osteoporosis, or mood disorders. However, further research is needed to establish long-term safety data, as well as the best protocol for its use. ■

Dearbhla Kelly, MB, BCh, BAO, MSc, MRCPI, is a renal specialist registrar with Beaumont Hospital, Dublin, Ireland.

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Table 1. Studies investigating steroid-minimization treatment strategies for MCD

Study	Design	Number of participants	Treatment protocol	Primary outcome	Results	Relapse rates	Safety profile
Kim et al. (24)	Pilot study (single center)	14	Tacrolimus 0.05 mg/kg twice daily and prednisolone 0.5 mg/kg/day (up to 40 mg/day) until remission for 16 weeks	Cumulative percentage of CR (defined as UPCR < 0.2 g protein/g creatinine) during 16 weeks	CR was achieved by 13/14 (92.9%) patients within 8 weeks.	Three of 14 (21.4%) patients had relapsed at 31 weeks, 36 weeks, and 40 weeks after treatment.	Three cases reported abdominal pain, diarrhea, or new-onset diabetes mellitus.
Li et al. (25)	Prospective RCT (8 centers in China)	119	Short-term intravenous methylprednisolone (0.8 mg/kg per day for 10 days) followed by a conventional tapering oral prednisone regimen vs. short-term intravenous methylprednisolone followed by tacrolimus (0.05 mg/kg/day) monotherapy for 36 weeks	Cumulative numbers of patients who experienced CR (decrease in proteinuria to ≤0.3 g/day) or PR (decrease in proteinuria to <3.5 g/day but >0.3 g/day)	Remission occurred in 51 of 53 (96.2%; all CR) glucocorticoid-treated patients and 55 of 56 (98.2%; 52 CR and three PR) tacrolimus-treated patients (p = 0.61 for remission; p = 0.68 for CR).	Relapse occurred in 49.0% and 45.5% of the glucocorticoid- and tacrolimus-treated patients, respectively (p = 0.71).	128 adverse events in the glucocorticoid group vs. 81 in the tacrolimus group; seven adverse events in the glucocorticoid group and two adverse events in the tacrolimus group were serious.
Medjeral-Thomas et al. (20)	Prospective, open-label RCT (6 centers)	50	Tacrolimus at 0.05 mg/kg twice daily (for 12 weeks, then tapered over a further 8 weeks) or prednisolone at 1 mg/kg daily up to 60 mg daily (for 16 weeks)	CR of nephrotic syndrome (UPCR < 50 mg/mmol) after 8 weeks of therapy	No significant differences in CR rates at 8 weeks (21 out of 25 [84%] for prednisolone and 17 out of 25 [68%] for tacrolimus cohorts; p = 0.32)	No significant difference in relapse rates (17/23 [73.9%] for prednisolone and 16/22 [72.7%] for tacrolimus cohorts)	18/25 patients experienced adverse events in the prednisolone cohort, and 20/27 did in the tacrolimus cohort (p = 0.99). There were four serious adverse events that required admission in the prednisolone and three in the tacrolimus cohorts (p = 0.99).
Chin et al. (21)	Prospective, open-label RCT (15 centers)	144	0.05 mg/kg twice-daily tacrolimus plus once-daily 0.5 mg/kg prednisolone vs. once-daily 1 mg/kg prednisolone alone for up to 8 weeks or until achieving CR	CR within 8 weeks (UPCR < 0.2 g/g)	CR within 8 weeks occurred in 53/67 patients (79.1%) receiving tacrolimus and low-dose steroid and 53/69 patients (76.8%) receiving high-dose steroid.	Significantly fewer patients relapsed on maintenance tacrolimus plus tapered steroid vs. tapered steroid alone (5.7% vs. 22.6%, respectively; p = 0.01).	49/67 (73.1%) in the combined tacrolimus and low-dose steroid group and 47/69 (68.1%) in the high-dose steroid group experienced adverse events (p = 0.52).

CR, complete remission; PR, partial remission; RCT, randomized controlled trial; UPCR, urine protein:creatinine ratio.