EDITORIAL

Levamisole: Standard or Intensive Therapy?

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Nephrotic syndrome has an estimated prevalence of 12-16 children per 100000 child population [1]. Almost one-half of these patients have frequent relapses or steroid dependence, which require management to prevent complications due to relapses as well as toxicity of corticosteroid therapy [2]. The initial management of patients with frequent relapses is with long-term prednisolone, which while effective, is associated with risks of steroid toxicity, particularly impaired growth and bone mineralization, and visual and metabolic complications. The use of steroid-sparing agents that enable reduction or cessation of corticosteroid therapy is therefore recommended [3,4]. Medications accepted for this purpose include levamisole, cyclophosphamide, mycophenolate mofetil (MMF), calcineurin inhibitors and rituximab. Evidence for their use is based on retrospective or prospective case series, few randomized placebo-controlled studies and even fewer comparative trials [5]. Guidelines from professional organizations recommend the use of steroid-sparing agents, but the order of therapy is not defined [3,4].

For more than three decades, levamisole has been considered effective and safe for preventing relapses of steroid-sensitive nephrotic syndrome [2-4]. The medication is available in Asia and marketed in few countries in Europe, but not in North- and South-Americas, and Africa. Data from multiple case series and meta-analysis of trials confirm that 1-2 year therapy with levamisole is steroid-sparing and results in about 50% reduction in relapses [5]. Despite clinical effectiveness, there is a limited evidence to explain the mechanisms of levamisole action. Some studies suggest that therapy results in upregulation of specific cytokines, including interleukin (IL)-8, IL-24 and those involving Th1-lymphocytes [6]. Glucocorticoid receptor expression and signaling on podocytes may be modulated by levamisole, and contribute to the response [7].

Two recent trials (available as conference abstracts) emphasize the efficacy of levamisole in relapsing nephrotic syndrome [8,9]. A study from our center compared the efficacy of alternate-day therapy with levamisole (n=73) to daily MMF (n=76) in reducing the frequency of relapses [8]. Over next 12 months, there were similar number of relapses in the two groups; relative relapse rate 1.27 relapses/person-year (95%CI 0.94, 1.74; P=0.12). The respective relapse rates were significantly reduced compared to the year preceding randomization in both levamisole (mean difference 2.1 relapses/person-year) and MMF (mean difference 2.4 relapses/person-year) (both P<0.0001) groups. The second is a double-blind placebo-controlled study that evaluated the efficacy of one year levamisole versus placebo therapy in 99 patients [9]. During follow-up, the time to relapse was increased in patients receiving levamisole compared to placebo (hazard ratio 0.22; 95% CI 0.11, 0.43; P=0.001). After 12-month treatment, 6% patients receiving placebo and 26% receiving levamisole were in remission (P=0.012). Moderate neutropenia, which reversed on discontinuation of treatment, occurred in 8%. Other side effects of prolonged therapy included elevation of transaminases and rare occurrence of small vessel vasculitis.

In this issue of *Indian Pediatrics*, Samuel, *et al.* [10] report a retrospective experience with levamisole in 95 patients with frequently-relapsing (n=62) and steroid-dependent (n=33) nephrotic syndrome. Therapy with alternate-day levamisole (2-2.5 mg/kg) was effective in 70 (73.7%). Out of 25 patients where alternate-day therapy with levamisole was not successful, a switch to daily levamisole administration at similar doses resulted in additional success in 14 patients. Therapy with standard alternate-day and the novel daily-therapy thus resulted in an overall benefit in 84 (88.4%) patients. Similar to others, results were better in the frequent relapsers than those with steroid-dependence [5,8,9]. No side effects were observed, although there is a possibility of under-reporting in the retrospective review. The effect of therapy was not sustained; one-half of patients showed frequent relapses on stopping levamisole.

The above observations are interesting and similar to recent reports that show promising results of daily therapy, should administration of alternate-day levamisole fail [11]. However, the literature is limited , and includes retrospective and prospective case series with significant risk of selection, performance and detection-bias; all of which might result in overestimation of effect-size by 20-35%. A placebo-controlled, multicenter double-blind randomized trial, stratified for steroid dependence, is required to examine if daily administration of levamisole is superior to alternate-day therapy. Given the observed effect, the study would require 130 patients per arm at 90% power, two-tailed alpha error of 5% and assumed attrition of ~10%. A careful prospective monitoring for adverse events would be necessary.

A note of caution! Five decades ago, the ISKDC empirically recommended 8 weeks of prednisone treatment for the initial episode of nephrotic syndrome; this increased to 12 weeks based on a randomized study by the APN [12]. Over the next 25 years, multiple open-label randomized studies (some with significant bias) showed that further prolongation of therapy was even better, resulting in meta-analysis based guidelines for ~7-month initial therapy, despite risks of steroid toxicity [13]. Over the past 4 years, the wheel has come 'full circle' with four high-quality multicenter double-blind trials affirming that 8-12 week initial therapy was enough with prolongation having no long-term benefits [14,15].

We need not follow the same path for levamisole. Multiple randomized trials affirm the satisfactory role of levamisole, administered on alternate days, as a steroid-sparing agent in patients with relapsing nephrotic syndrome. Until results from placebo-controlled studies confirm the benefits and safety of daily over alternate-day levamisole therapy, we suggest that pediatricians continue to follow standard guidelines for treatment.

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