Is Two Month Initial Prednisolone Treatment for Nephrotic Syndrome Inferior to Longer Duration Therapy ?

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SUMMARY

This multi-center randomized trial [1] in children with steroid sensitive nephrotic syndrome (NS) compared prednisolone therapy for 2 months *versus* 6 months. Authors evaluated time to occurrence of frequent relapse, time to first relapse, and various adverse events in 255 children (1-15 years) from 90 Japanese hospitals presenting with first episode of NS. Those who achieved remission within 3 weeks of prednisolone therapy were randomized to either 6 months therapy [60 mg/m^2 daily for 4 wk, gradually (4 weekly) tapering alternate day doses for next 24 wk] or 2 months therapy (60 mg/m^2 daily for 4 wk, 40 mg/m^2 alternate day for 4 wk) with oral prednisolone. Children were followed up for at least 2 years. The authors reported comparable (i) time to frequent relapses (RR 0.86, 95% CI 0.64, 1.16), (ii) episodes of relapse (RR 0.92, 95% CI 0.75, 1.14), (iii) frequent relapses (RR 0.99, 95% CI 0.72, 1.38), (iv) time to first relapse, (v) relapse rate per person-year, and (vi) adverse effects (hypertension, cushingoid facies, glaucoma, and elevated hepatic enzymes). The authors also presented a meta-analysis comparing trials using 2-3 *versus* 5-6 months therapy, and reported comparable results. They suggested that 2 months of prednisolone is not inferior to 6 months therapy.

COMMENTARIES

Contemporary Researchers' Viewpoint

Most patients with steroid sensitive nephrotic syndrome show highly satisfactory renal outcomes [2]. While morbidity due to infections has declined with rapid diagnosis and use of vaccines, toxicities associated with repeated course of corticosteroids remain a major concern in managing patients with frequent relapses or steroid dependence. While the International Study for Kidney Diseases in Children (ISKDC) arbitrarily proposed that the initial corticosteroid therapy comprise of 4-weeks daily followed by 4-weeks intermittent therapy, refinements have been proposed over the last four decades. A randomized controlled trial in 1993 showed reduced relapse rates on prolonging therapy from 8 to 12 weeks [3]. Further randomized studies confirmed these findings and suggested that extending initial therapy to 6-months was even better. Results from a Cochrane meta-analysis showed that therapy for 6-months *versus* 3-months was associated with reduced risk of frequent relapses (RR 0.55; 95% CI 0.39,0.80) and fewer relapses per year. The review suggested an inverse relationship between the risk for relapse and duration of induction therapy, such that the relative risk for relapse at 12-24 months would fall by 11% of baseline relapse rate for every one month increase in duration of therapy from 2-7 months [4]. While studies included in the analysis had methodological concerns, the results unequivocally suggested that *(i)* 12-weeks therapy was better than 8-weeks, and *(ii)* therapy could be extended to 6-months with further benefits in rates of sustained remission and reduced frequency of relapses.

Three recent well designed randomized studies contest the above view. A multicenter placebo-controlled parallel group trial from Netherlands, on 150 children, showed no differences in the cumulative proportion of children with frequent relapses (45 *versus* 50%) or any relapse (77% *versus* 80%) when initial therapy was prolonged from 12 to 24 weeks without increasing the cumulative dose [5]. Similarly, a randomized placebo-controlled blinded trial conducted across 5 centers in North India on 181 patients randomized to receive 6 or 3 months of prednisolone differing in cumulative dose by 739 mg/m^2, showed no differences in the frequency of relapses at one year, hazard for frequent relapses, and proportions with sustained remission or steroid adverse effects [6]. *Post-hoc* subgroup analysis showed that children younger than 3 year might benefit from 6 months therapy with reduced

risk for first relapse, but not for frequent relapses, suggesting that prolonged therapy requires closer evaluation in this subgroup. The open label multicenter randomized trial from Japan, published simultaneously with the Indian study, examined the non-inferiority of 2 months to 6 months therapy with prednisone at higher cumulative dose (2240 *versus* 3840 mg/m^2) in 255 patients, 1-15 yr-old, followed for 2 years [7]. The definition for relapse used in this study, 2+ or more proteinuria, was liberal than that used otherwise, which may have led to overestimating the rates of relapses and frequent relapsers. Based on these results, the authors conclude that initial steroid therapy for two months, despite less medication exposure, was not inferior to 6 months treatment in affecting the rates of frequent relapses.

Results from these three studies that enrolled almost 600 patients on two continents emphasize that prolongation of initial therapy to 6 months is not useful in modifying the course of the disease, or reducing subsequent needs for corticosteroids and steroid-sparing agents. The Indian study, but not the others, showed that the benefit of extended initial therapy was limited to the period while the steroids were being administered [1,5,6]. Since the intent of intensification of therapy is to alter the disease course rather than delaying the first relapse, lower rates of relapses during steroid tapering alone should not lead to consideration of prolonged therapy. Furthermore, the benefits of therapy prolongation should be balanced against the risk of corticosteroid adverse effects. Given the current data, prolongation of initial therapy beyond that proposed by the ISKDC [2] and the APN [4] is perhaps not justified. Recommendations of the Indian Society of Pediatric Nephrology [7], Kidney Diseases Improving Global Outcomes [8] and the Canadian Society of Pediatric Nephrology [9] are likely to remain unchanged in endorsing 12 weeks therapy for the initial episode of nephrotic syndrome.

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Pediatric Nephrologist's Viewpoint

This multicentric open-labeled non-inferiority trial, undertaken in Japan, randomized 255 children with the first episode of nephrotic syndrome, to receive either 2 month or 6 month therapy with oral prednisolone. The end points of the initial course of therapy were similar in both groups, with a lower mean cumulative dose of steroids in the 2 month therapy group compared to the 6 month therapy arm. In the past decade, as evident in the Cochrane reviews, children with first episode of nephrotic syndrome, treated with prednisone for at least three months resulted in fewer relapse rates by 12 to 24 months with an increase in benefit being demonstrated for up to seven months of treatment compared to two months therapy (ISKDC regime) [4]. In contrast to this finding, certain studies [5,10] failed to show benefit of prolonged duration of prednisolone in reducing the frequency of relapses, despite maintaining equal cumulative dose of steroids between groups in the Dutch study [5]. Recently, a well-designed, placebo controlled randomized trial in Indian children revealed that extending initial prednisolone treatment from 3 to 6 months is not effective in modifying the course of disease and reducing subsequent need for corticosteroids, within a year of follow up, in children with nephrotic syndrome [6].

In clinical practice, the major challenge in treating nephrotic syndrome is to reduce the rate of relapses and minimize the adverse effects of steroid therapy. While there seems to be new evidence that supports the hypothesis that initial duration of steroid therapy has limited impact on relapse rates, a few essential points need to be considered at this juncture. First, the interpretation of relapses in most studies is based on follow up period of 12-24 months, which is relatively a short time span compared to the well-known highly variable clinical course of nephrotic syndrome that lasts for more than a decade. The impact of initial cumulative dose of steroid therapy, besides the duration, needs further evaluation. Second, it would be essential to consider the baseline rate of relapse in a particular community, as most relapses are triggered by infections that may be independent of the duration or dose of initial steroid therapy. Third, we need clarity on the precise effect of age of the child at onset of nephrotic syndrome, on the occurrence of relapses. To conclude, though we may not be ready with a recommendation, we are encouraged to be conscious of the fact that intentional prolongation of initial steroid therapy, though may not predispose to higher steroid toxicity, may not be as beneficial as we believed it to be, in reducing relapse rates in nephrotic syndrome.

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Evidence-based-medicine Viewpoint and Systematic Review

Relevance: Some decades back, ISKDC advocated an eight-week steroid regimen for induction and maintenance of remission in children with nephrotic syndrome (NS)

[11]. This was followed for several years, whereupon it was observed that while remission was achieved in most children, the majority relapsed and a quarter to half develop frequent relapses [2,12,13]. Therefore, trials comparing longer (≥ 3 mo) therapy with the then-standard two months regimen were undertaken. These trials and subsequent systematic reviews including a Cochrane review last updated in 2007 [4] suggested that longer duration of therapy was associated with better outcomes. The relatively low methodological quality of trials on which this conclusion was based, and the natural concern about adverse effects of therapy with longer steroid regimen prompted some investigators to revisit the issue. An additional confounding factor is that longer duration of therapy is associated with higher total dosage of steroid; therefore it is difficult to determine whether longer duration or higher dose or both together account for better outcomes with such regimens. The outdated Cochrane review [4,14] argued in favor of increased duration (rather than higher dose). There is uncertainty about the optimal steroid regimen that could achieve the triple goal of inducing remission, preventing relapses, and ensuring safety in terms of avoidance of steroid-related adverse events. Against this backdrop, the trial by Yoshikawa, *et al*. [1] is very timely and relevant.

Critical appraisal: Two angles need exploration viz (*i*) appraisal of the trial itself, and (*ii*) contextualizing the evidence from this trial, in terms of the clinical question *viz* what is the optimal steroid regimen in children with NS?

In terms of methodological quality, the trial utilized an adequate method for generation of randomization sequence. Allocation concealment was not described and blinding was absent. Of 255 enrolled children, the authors could report outcomes in 246 with comparable loss in both groups. Unlike most such trials, the authors chose a non-inferiority design with its associated (appropriate) calculation of sample size. They chose risk ratio of time to frequently relapsing NS (FRNS) as the primary outcome, rather than the more commonly presented frequency of relapses or FRNS. Standard definitions were used for the various conditions. Steroid adverse effects were comparable between the groups, generally occurred early, and were transient. The authors concluded that this indicates that the shorter duration could be recommended since it delivers a lower total dose. However, this conclusion is not supported by the data in the trial. The meta-analysis presented as a Supplement contains some methodological errors (incorrect data entry), hence need not be considered.

This necessitates a fresh look at the available evidence. As 3 months therapy is the current recommended standard of care [7-9,15], the following comparisons of efficacy are meaningful: (*i*) 3 months therapy versus >3 months; (*ii*) 3 months versus 2 months; and (*iii*) 2 months versus >2 months. It is also important to compare trials using the same dose (over different durations) as well as same duration (with different doses). Therefore, a fresh systematic review was undertaken searching PubMed and the Cochrane Library. Two sets of searches were conducted through PubMed using the terms: "(nephrotic syndrome) AND steroid" with filters: *Meta-Analysis, Systematic Reviews, Randomized Controlled Trial, Child: birth-18 years;* and "(nephrotic syndrome) AND steroid AND duration" without any filters. The Cochrane Library was searched using the term "nephrotic syndrome" without any filters. Seventeen trials [1,12-27] were identified that compared different durations and/or dose of prednisolone therapy and evaluated relapse as an outcome over a period of at least 12 months follow-up (***Web Table* I**). One trial [27] comparing 12 months *versus* 5 months therapy was not included.

Summary of the meta-analyses of efficacy (risk ratio, random effects model) is presented in ***Table* I**, showing that therapy >3 months (with higher steroid dose) is more efficacious than 3 months. Limited data suggest that longer duration or higher dose alone did not make a difference. Therapy for 3 months was comparable to 2 months (with or without higher total dose). When therapy >2 months was compared against 2 months, the former appeared more efficacious. These findings are contrary to the results in Yoshikawa's trial [1]. While the overall results are in agreement with the outdated Cochrane review [4], the assertion therein that longer duration rather than higher dose is responsible for greater efficacy [4,15], could not be substantiated. However, it should be remembered that the quality of individual trials in the meta-analysis leaves a lot to be desired.

It is also important to consider safety issues. The diverse sets of data made meta-analysis difficult. However, almost all the trials showed comparable frequency of adverse events. More importantly, most adverse events occurred during the initial (more intensive) phase of therapy, wherein the dosage and duration are more comparable. An indirect point to note is that the lower efficacy of shorter duration/lower total dose may be associated with more relapses and hence more doses of prednisolone, thereby increasing the potential for adverse events.

Extendibility: The issues of optimal management of childhood nephrotic syndrome and the ideal steroid regimen are relevant to the Indian setting. Although the results of the trial cannot be extended to our setting, the

TABLE I SUMMARY OF META-ANALYSES

Comparison	*Outcome*	*Result (RR, 95% CI)*
>3 mo (with higher dose) *vs* 3 mo therapy	Relapse	0.58 (0.42, 0.79); 5 trials, 604 participants, I^2=73% (*Fig*. 1A)
	Frequent relapses	0.68 (0.54, 0.85); 5 trials, 604 participants, I^2=45% (*Fig*. 1B)
>3 mo *vs* 3 mo therapy (with same total	Relapse	1.03 (0.86, 1.24); 1 trial, 126 participants (*Fig*. 2A)
dose in both groups)	Frequent relapses	1.11 (0.77, 1.60); 1 trial, 126 participants (*Fig*. 2B)
Higher *vs* lower steroid dose (administered	Relapse	0.63 (0.42, 0.94); 1 trial, 59 participants (*Fig*. 3A)
over same duration i.e 3 mo)	Frequent relapses	0.69 (0.35, 1.37); 1 trial, 60 participants (*Fig*. 3B)
3 mo (with higher dose) *vs* 2 mo therapy	Relapse	0.91 (0.61, 1.38); 3 trials, 99 participants, I^2=62% (*Fig*. 4A)
	Frequent relapses	0.83 (0.55, 1.27); 3 trials, 99 participants, I^2=2% (*Fig*. 4B)
>3 mo (with higher dose) *vs* 2 mo therapy	Relapse	0.71 (0.58, 0.88); 6 trials, 498 participants; I^2=48% (*Fig*. 5A)
	Frequent relapses	0.81 (0.65, 1.00); 6 trials, 742 participants, I^2=40% (*Fig*. 5B)
3 mo *vs* 2 mo therapy (with same total dose)	Relapse	1.09 (0.88, 1.36); 1 trial, 112 participants (*Fig*. 6A)
	Frequent relapses	1.14 (0.78, 1.66); 1 trial, 112 participants (*Fig*. 6B)

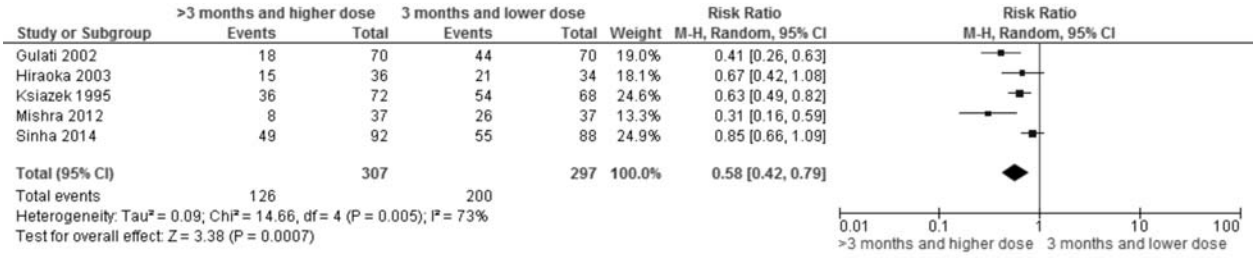

FIG 1A *Comparison of >3 mo (with higher dose) vs 2 mo therapy. Outcome: Relapse*

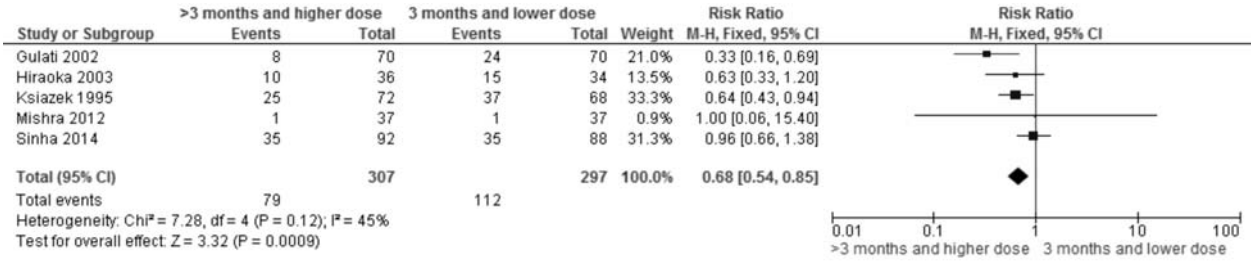

FIG 1B *Comparison of >3 mo (with higher dose) vs 2 mo therapy. Outcome: Frequent relapses*

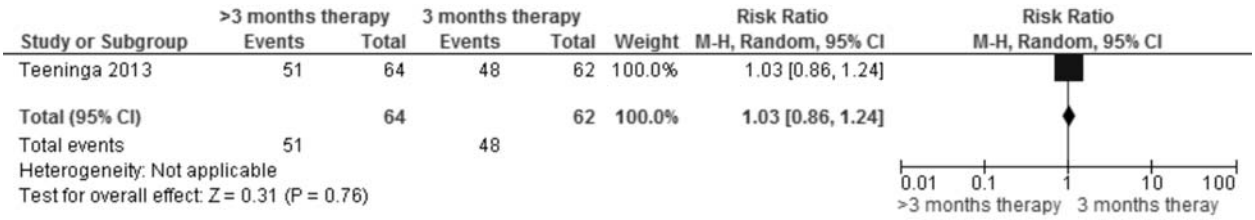

FIG 2A *Comparison of >3 mo vs 3 mo therapy (with same total dose in both groups). Outcome: Relapse*

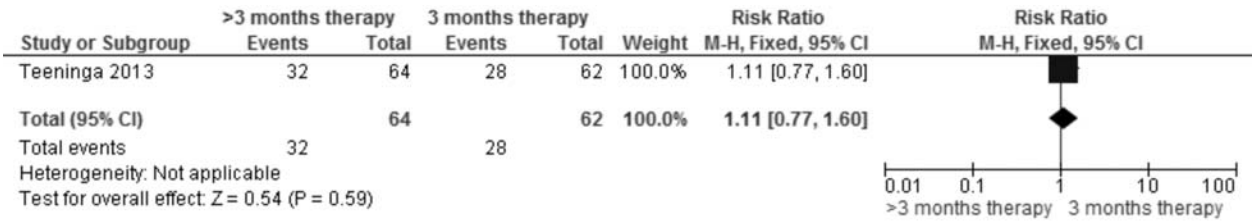

FIG 2B *Comparison of >3 mo vs 3 mo therapy (with same total dose in both groups). Outcome: Frequent relapses*

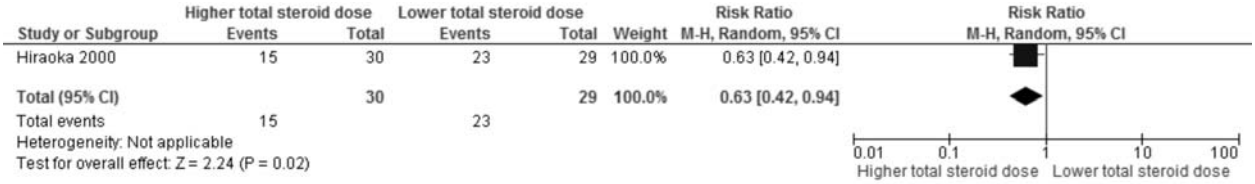

FIG 3A *Comparison of Higher vs Lower steroid dose (administered over same duration i.e 3 mo). Outcome: Relapse*

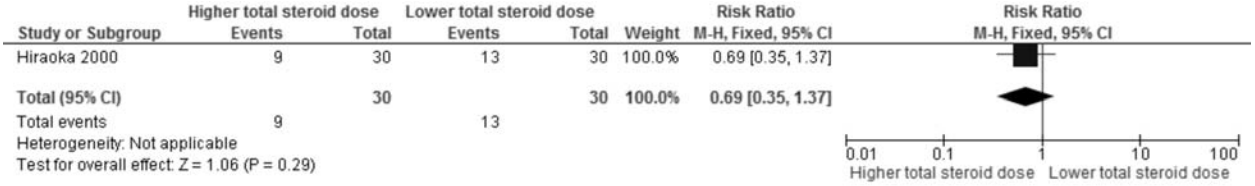

FIG 3B *Comparison of Higher vs Lower steroid dose (administered over same duration i.e 3 mo). Outcome: Frequent relapses*

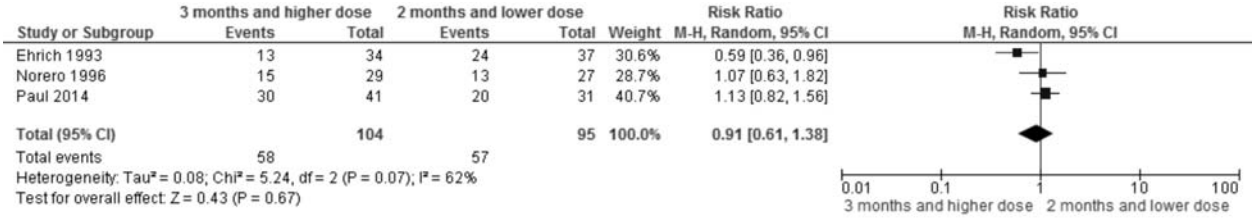

FIG 4A *Comparison of 3 mo (with higher dose) vs 2 mo therapy. Outcome: Relapse*

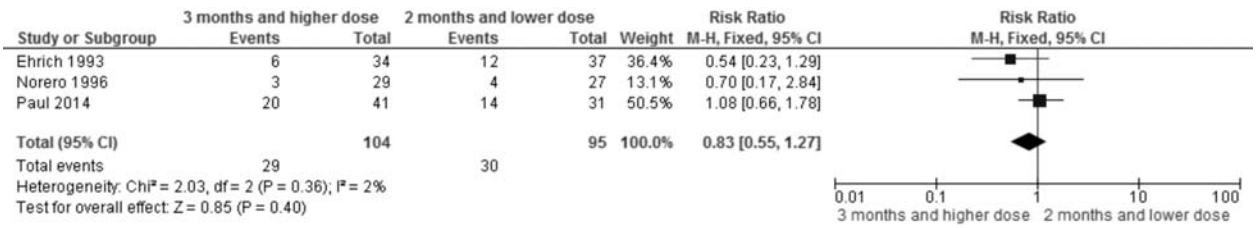

FIG 4B *Comparison of 3 mo (with higher dose) vs 2 mo therapy. Outcome: Frequent relapses*

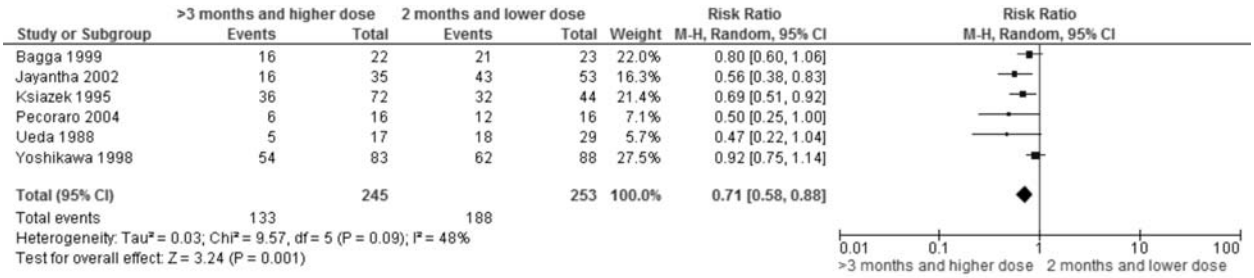

FIG 5A *Comparison of >3 mo (with higher dose) vs 2 mo therapy. Outcome: Relapse*

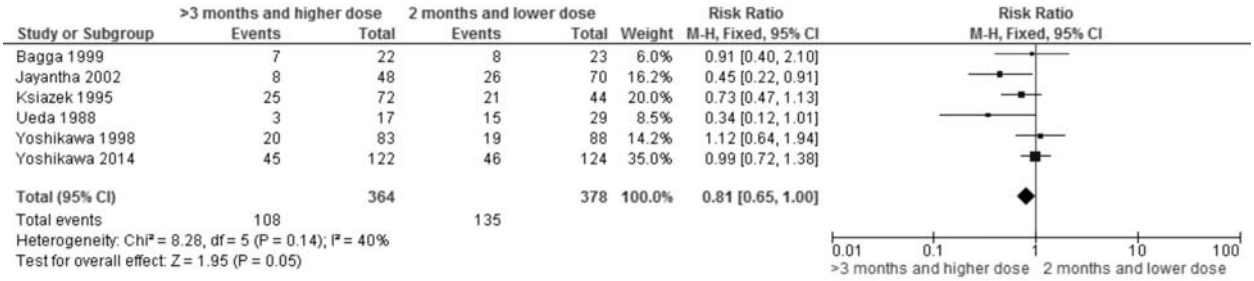

FIG 5B *Comparison of>3 mo (with higher dose) vs 2 mo therapy. Outcome: Frequent relapses*

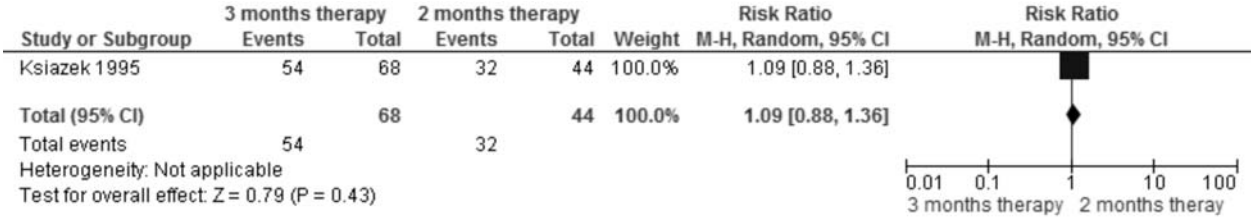

FIG 6A *Comparison of 3 mo vs 2 mo therapy (with same total dose). Outcome: Relapse*

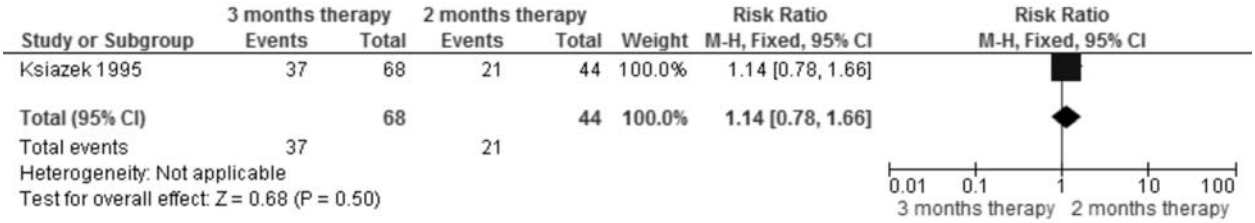

FIG 6B *Comparison of 3 mo vs 2 mo therapy (with same total dose). Outcome: Frequent relapses*

findings of the new systematic review presented here are applicable.

Conclusions: Although the trial suggests that 2 months steroid therapy may be non-inferior to 6 months therapy, the overall conclusion based on evaluation of all available data (through a fresh systematic review) suggests that prednisolone therapy longer than 3 months (with higher dose) is more efficacious than that for 3 months or less.

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