Pediatr Nephrol (2017) 32:99–105
DOI 10.1007/s00467-016-3458-6

ORIGINAL ARTICLE

Use of a low-dose prednisolone regimen to treat a relapse of steroid-sensitive nephrotic syndrome in children

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Received: 23 March 2016 / Revised: 25 June 2016 / Accepted: 28 June 2016 / Published online: 27 September 2016

Abstract
Background Relapses of nephrotic syndrome are common and are treated with a course of prednisolone (2 mg/kg/day or 60 mg/m^2/day). This is associated with major adverse effects including diabetes, weight gain, hypertension and behavioural problems. This study is a retrospective review examining the success of treating relapses in steroid-sensitive nephrotic syndrome (SSNS) with low-dose prednisolone and the consequences on subsequent relapse rates. Furthermore, a follow-up study looked at the side-effect profile during treatment with high- versus low-dose prednisolone.
Methods Between January 2012 and July 2013, all well children with SSNS presenting with a relapse were advised to start 1 mg/kg prednisolone daily for a maximum of 7 days. In July 2015, we compared the side-effect profile of prednisolone therapy using the parent proxy PedsQL questionnaire for quality of life (QoL).
Results Fifty patients were included in the study, with a total of 87 relapses. Sixty-one of the 87 relapses (70 %) responded within a week. Treating relapses with a reduced dose of steroids did not adversely affect the relapse rate in the 6 months preceding and following the current relapse (1.01 vs 0.86, $p = 0.3$). Fifteen parents completed the PedsQL questionnaire. Comparison of scores in each category showed significantly higher values in each domain during treatment with low-dose prednisolone compared with high-dose treatment (35.6 vs 18.3, $p < 0.0001$; 31.1 vs 15.0, $p < 0.001$; 38.3 vs 20.1, $p < 0.0001$).
Conclusion A low-dose prednisolone regimen was successful in achieving remission in 70 % of relapses of children with SSNS, without adversely affecting the relapse rate. Parent-completed QoL questionnaires showed significantly higher scores on low-dose treatment, indicating better QoL.

Keywords Steroid-sensitive nephrotic syndrome (SSNS) · Low-dose prednisolone · PedsQL

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Introduction

Idiopathic nephrotic syndrome (NS) is the most common glomerular disease of childhood [1], with an incidence of 2–4 cases per 100,000 children in the UK. Initial treatment is with high-dose oral corticosteroids (prednisolone or prednisone), with which more than 90 % make a complete recovery, earning the label steroid-sensitive nephrotic syndrome (SSNS). This is a relatively benign condition with the majority achieving spontaneous long-term remission in later childhood. However, in early childhood, 70–80 % of these children go on to develop further relapses, and of these, about 50 % develop frequently relapsing disease [2]. Treatment of these relapses requires further courses of high-dose corticosteroids, and a significant proportion of children go on to require long-term, low-dose maintenance corticosteroid therapy to reduce the frequency of relapses. A number require additional immunosuppressive agents, such as levamisole, ciclosporin, cyclophosphamide, mycophenolate mofetil (MMF), tacrolimus and rituximab.

Relapses of NS are associated with major complications such as sepsis, thrombosis and dyslipidaemia. During the lifetime of the disease most patients will have been exposed to a significant cumulative dose of corticosteroids. In more recent years, there have been an increasing number of studies

looking at the effects of high-dose corticosteroids on behaviour [3–7], concluding that there was a high prevalence of behavioural disturbances in children with SSNS. The largest of these studies [8] found that this was most marked in patients with frequent relapses or steroid dependence, both for internalising and externalising behavioural patterns.

These studies emphasise the need to minimise corticosteroid use in children with NS so as to achieve and sustain remission without an increase in adverse effects. However, owing to a lack of data from randomised controlled trials, a Cochrane review [9] concluded that there was no defined optimal way to treat a relapse of SSNS.

The current practice in the UK for those with infrequently relapsing SSNS, is to treat relapses with this high-dose prednisolone regimen of 60 mg/m^2/day or 2 mg/kg/day to a maximum of 60 mg/day until they are in complete remission for at least 3 days. Following this, the recommendation is to give 40 mg/m^2 on alternate days or 1.5 mg/kg on alternate days to a maximum of 40 mg every other day for at least 4 weeks before stopping or tapering the dose. This is in accordance with the Kidney Disease Improving Global Outcomes (KDIGO) guidelines [10] based on the arbitrarily determined regimen of the International Study of Kidney Disease in Children (ISKDC) from the 1960s.

In those children who have frequently relapsing SSNS or steroid-dependent nephrotic syndrome (SDNS), guidelines recommend high-dose prednisolone therapy until in remission for at least 3 days, followed by alternate-day prednisolone for at least 3 months. This should be tapered down to the lowest dose required to maintain remission without major adverse effects. In the subgroup of children in whom alternate-day prednisolone is not effective, daily prednisolone should be given in the lowest dose possible to maintain remission.

From our anecdotal experience we have observed that a cohort of patients appeared to be very sensitive to steroids. In this cohort of patients we started to question whether a high-dose steroid regimen was truly required to treat a relapse. There are currently no published data looking at the efficacy of an alternative lower-dose regime in treating a relapse in such children. We decided to trial an alternative low-dose steroid regime, 1 mg/kg for the treatment of a relapse in SSNS, which continues to be the standard of care at present for suitable patients. This study is a dual-centre retrospective analysis of the outcome of a low-dose prednisolone regime in treating relapses of SSNS in children and its subsequent effect on the relapse rate and behaviour.

Materials and methods

Study design

Our first study was a retrospective case note review of SSNS children presenting with a relapse at Great Ormond Street Hospital or Royal London Hospital, between January 2012 and July 2013, treated with a new low-dose prednisolone regimen introduced in January 2012. This was done as part of a strategy to empower families to test and commence therapy with prednisolone at home without having to wait for a medical review.

A relapse was defined as 3+ proteinuria on dipstick testing for 3 consecutive days, or at least 2+ proteinuria for 5 consecutive days. Remission was described as 0 to trace proteinuria on dipstick testing for at least 3 days.

We collected baseline patient data including the age at disease onset, gender, ethnic background, relapse rate and maintenance medication. We then followed patients for a minimum period of 6 months to examine the relapse rate after initiating a lower prednisolone regimen and any changes to the maintenance medication.

Patients

Any child who presented with a relapse was assessed for evidence of significant oedema and/or intravascular depletion at presentation by ascertaining from the parents fluid intake and urine output. If there were any uncertainties, patients were reviewed locally or in the nephrotic clinic and excluded from the study only if they showed these features. All those included were treated with a modified low-dose prednisolone regime, namely 1 mg/kg/day up to a maximum of 40 mg/day for a minimum of 7 days (this dose was continued even if they went into remission before completing 7 days of treatment). This included patients on no medication, those on prednisolone or a corticosteroid-sparing agent, and those on a combination of both. Once the patient was in remission and/or had completed 7 days of therapy, the dose of prednisolone was gradually tapered over a month. If the patient failed to go into remission within 7 days of starting therapy or developed progressive oedema or symptoms of intravascular depletion, they were medically reviewed and the prednisolone dose was increased to the standard regime dose of 2 mg/kg/day. All patients were advised to keep a diary of their treatment and symptoms and were followed up by telephone review by the Nephrotic Nurse Specialist or in clinic.

Prednisolone side effects profile

We conducted an additional study asking patients and their families to describe the side effects whilst on different steroid regimens.

In July 2015, we randomly selected 15 patients from our initial database who had on different occasions received treatment with both high-dose (2 mg/kg/day) and low-dose (1 mg/kg/day) prednisolone for a relapse of their SSNS. Patients were included if they were currently being treated for a relapse or had been recently treated (in the preceding 3-

month period). Parents were asked to complete a 23-item PedsQL™ 4.0 Generic Core Scale, which is a standardised multi-dimensional quality of life questionnaire. Patients recruited from the outpatient clinic were given an age-appropriate parent-proxy questionnaire to complete. The remainder were sent the questionnaires via email or post. Informed consent for the study was obtained verbally by the research nurse. Parents were asked to complete separate questionnaires for the most recent episode of relapse that had been treated with low-dose prednisolone and that with high-dose prednisolone, thereby using patients as their own controls. When parents failed to respond to the email or letter, they were telephoned and the scores were obtained verbally.

The QoL questionnaire that was used was the parent-proxy report format of the PedsQL™ 4.0 (Pediatric Quality of Life Inventory™ Version 4.0). This 23-item PedsQL™ 4.0 Generic Core Scales has four multidimensional scales that include: Physical Functioning (8 items), Emotional Functioning (5 items), Social Functioning (5 items), and School Functioning (5 items) [11]. The questionnaire is practical, taking approximately 5 min to complete [12].

Study outcome

The primary outcome measure of the first study was the proportion (or percentage) of patients who went into remission following a low-dose prednisolone regimen. Secondary outcome measures were the time taken to go into remission and the relapse rate before and after initiating the lower prednisolone regimen. The primary outcome of the second study was the patient- and family-perceived prednisolone side effects profile on a high- and a low-dose prednisolone regimen.

Sample size and statistical analysis

The data were collected over a defined time period, which gave us a fixed sample size of 87 relapses in 50 patients. With this fixed sample size, and presuming that 70 % of the patients would respond to this treatment, the precision of the estimated proportion is calculated at 0.10. This gives a relatively wide 95 % confidence interval (CI) of 0.60–0.79.

Continuous data were expressed as the means ± standard deviation (SD) and by the difference in means with 95 % CI. Statistical analyses included the paired *t* test to compare groups. A p value of <0.05 was considered to be statistically significant, and <0.01 highly significant. In addition, for the analysis of the PedsQL questionnaire, effect sizes were calculated to determine the magnitude of the differences observed [13]. Effect size as used in these analyses was calculated by taking the difference between the means of the two groups divided by the pooled standard deviation. Effect sizes for differences in means were designated as small (0.20), medium (0.50) and large (0.80). Statistical analyses were conducted using IBM SPSS Version 22.0 for Windows.

Results

Fifty patients were included in the first study, with a total of 87 relapses. Patients were aged between 3 and 17 years. Thirty-five of these patients were male, and 15 were female (2.3:1). Of these, 26 patients were white and a further 20 were Asian, 19 of whom were of South Asian origin. The remaining 4 were black. Table 1 (below) shows the baseline characteristics of the patient and disease.

Sixty-eight of the relapses were not associated with any oedema. In the remaining 19 there was mild oedema only, with no evidence of haemodynamic instability.

Response to treatment

In 61 out of 87 relapses (70 %), patients responded to the low-dose prednisolone regimen, showing complete remission within 7 days. In a further 6 (7 %), treatment was extended for a maximum of 3 more days, by which time they were all in complete remission. The decision to extend treatment was made because they all showed partial remission over the 7-day period, with a significant reduction in proteinuria. The remaining 20 (23 %) only responded when their prednisolone dose was increased to the standard dosage of 2 mg/kg. Timing of initiation of therapy was not delayed in the non-responders group compared with those who had responded.

Medication at time of relapse

The background medication that the patients were on is shown in Fig. 1. Of the non-responders, only 3 of the 20 (15 %) were on no medication and 60 % (12 out of 20) were already on

Table 1 Patient and disease characteristics

	Mean ± SD	Median	Range
Age (years)	9.1 ± 3.9	8.5	3.2.17.8
Age at onset (years)	3.8 ± 2.7	3	0.6–11.2
Weight at time of relapse (kg)	41.2 ± 20.2	35	14–114
Number of relapses (in previous 6 months)[a]	1.0 ± 1.1	1	0–4

[a] Data were not available for 3 of the 87 episodes

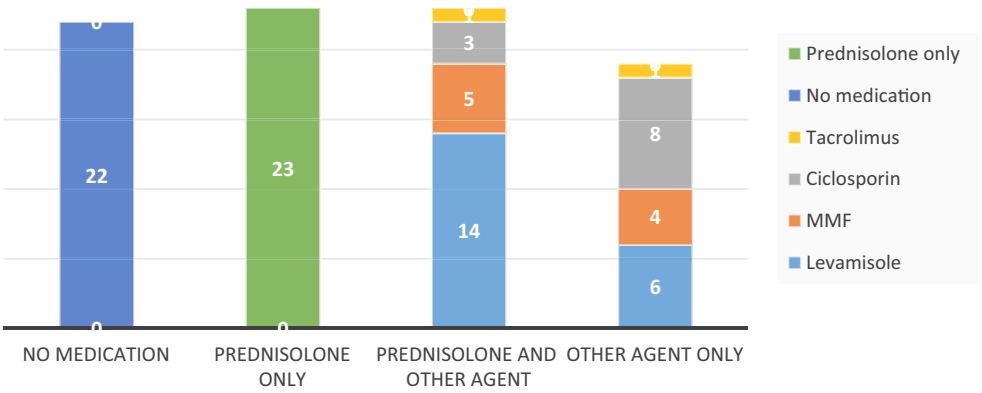

Fig. 1 Medication at the time of relapse. *MMF* mycophenolate mofetil

low-dose, alternate-day prednisolone, with or without another agent. Fig. 2 shows the response rate in relation to their baseline regimen.

Prednisolone dosage

For those already on long-term prednisolone at the time of the relapse (Fig. 3), the mean dose was 0.3 ± 0.2 mg/kg on alternate days (median 0.3, range 0.01–1.0). The mean dose of prednisolone used to treat a relapse was 0.75 ± 0.25 mg/kg (median 0.8, range 0.25–1.15), which is lower than the targeted dose of 1 mg/kg because of a maximum dose of 40 mg being used.

Effect on relapse rate

The mean number of relapses in the 6 months preceding the current relapse and the following 6 months were compared (Table 2). A paired *t* test comparison of the means (1.01 vs 0.86) gave a *p* value of 0.30 (95 % CI −0.14 to 0.45). Therefore, we can conclude that a low-dose prednisolone regimen did not compromise the relapse rate in these children. The mean number of relapses in the preceding 6 months was slightly higher in the non-responders group (1.25) compared with the overall mean of 1.01.

Five patients that were treated with rituximab around the time of relapse all had no further relapses in the following 6 months. Furthermore, several patients were started on other immunosuppressive agents during this time period, which may have had an effect on the rate of relapse. Ten of the patients were given a course of cyclophosphamide during the data collection period and in these patients there was a significant reduction in the number of relapses (mean 2 ± 1.4 vs 0.3 ± 0.7), *p* value =0.006. However, even excluding these 15 patients, a paired *t* test comparison of the means (0.81 vs 0.97) gave a *p* value of 0.28, similar to the value obtained for the overall population.

Side effects of prednisolone therapy

In our second study, using the PedsQL questionnaires, 15 parents were approached and completed the questionnaires. Patients were aged 3–14 years (mean 8.7 years). Questionnaires completed included 1 for the group aged 2–4 years, 5 for the group aged 5–7 years, 6 for the group aged 8–12 years, and 3 for the group aged 13–18 years. Five of

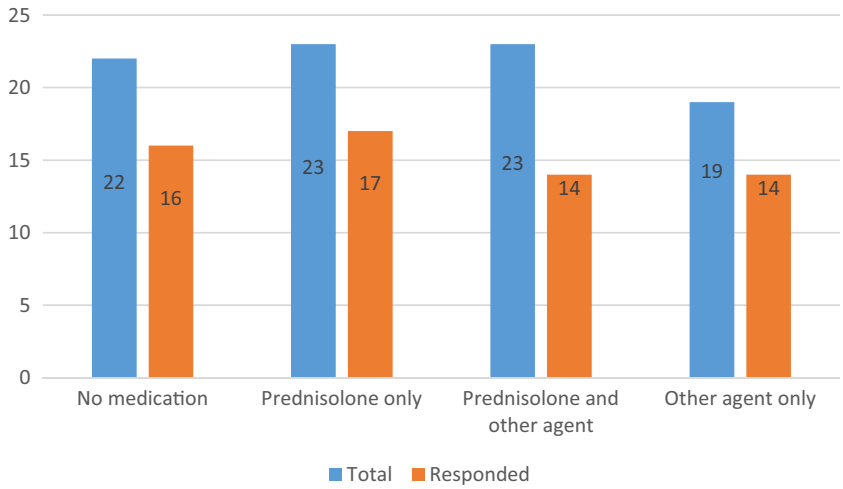

Fig. 2 Background medication of responders

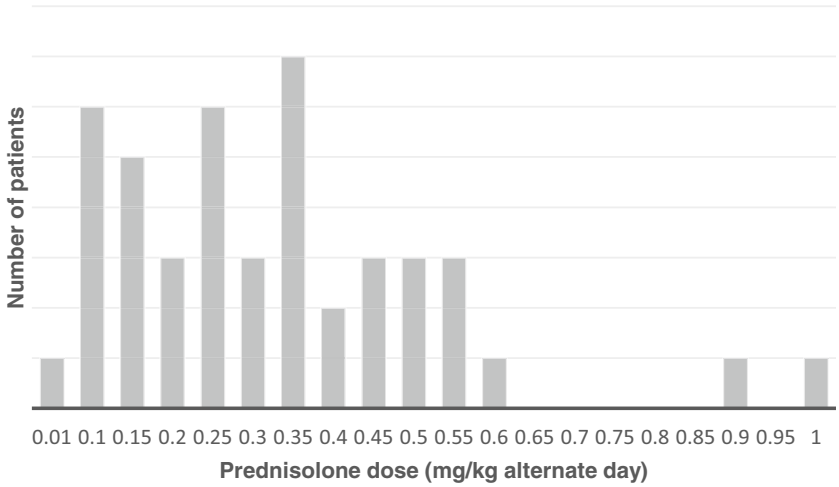

Fig. 3 Dose of prednisolone already administered

these questionnaires were completed by the parents in the clinic and the remaining 10 over the telephone. Of the 15 patients, 7 were South Asian, 6 White British and 2 White European. Two of the questionnaires were filled in with the help of an interpreter in the clinic.

The comparison of scores in each category, namely the Physical Health Summary Score and Psychological Health Summary Score, and the individual multifunctioning scales, showed significantly higher values in each domain during treatment with low-dose prednisolone compared with high-dose treatment (Table 3). This difference was consistent within age groups. The comparison of means and SD between the summary scores is shown in Table 4. Effect sizes for the difference in means in all three categories were large, i.e. 1.20 (total health score), 0.83 (physical health summary score) and 1.34 (psychological health summary score).

Discussion

Children with SSNS have an 80–90 % chance of having one or more relapses [14, 15] and each of these relapses is associated with an increased risk of complications, along with parental and patient anxiety. Children are unable to attend school during relapses, leading to impaired education performance and parental absence from work. Furthermore, each of these relapses is conventionally treated with high-dose prednisolone, which carries its own risk of side effects. These recommendations from the KDIGO Glomerulonephritis Workgroup, 2012 [10], are based on only a few randomised controlled trials and the dose is one that has been used empirically by the ISKDC since the 1960s without being examined further in any future trials. Therefore, although these doses are recommended, the quality of evidence supporting these data is very low.

There are no published data in the literature regarding the use of a lower dose prednisolone regimen to treat a relapse once it has occurred. From our anecdotal experience we have observed that a certain cohort of patients are extremely sensitive to steroids and we therefore wanted to see the effect of treating relapses in these patients with a lower dose of prednisolone. There was also concern regarding steroid toxicity and it was noted that a significant proportion of patients were reluctant to commence high-dose prednisolone, thereby affecting the compliance rate. For this reason, we conducted a study to look at the effectiveness of treating a relapse of SSNS with such a regimen, and its subsequent effect on the relapse rate.

Seventy percent of the relapses included in the study responded to the low-dose prednisolone regimen showing complete remission within 7 days and a further 7 % responded by 10 days. No obvious common characteristics were noted in the group of non-responders. However, it was observed that only 3 of those 20 (15 %) were on no medication compared with 19 out of 67 (28 %) in the group that did respond. Furthermore, 12 of the 20 non-responders (60 %) were already on alternate-day prednisolone, with or without another agent. This implies that this group of patients may have SSNS that was more difficult to treat than that of the group that responded to low-dose treatment. Importantly, none of the patients that failed to respond showed a deterioration in clinical state when reviewed.

On a note of caution, this study included a mixed cohort of children, some of whom were on background alternate-day prednisolone, whilst others were on additional immunosuppressive

Table 2 Relapse rate before and after a low-dose prednisolone regimen

	Pre-relapse	Post-relapse
Mean ± SD	1.0 ± 1.1	0.86 ± 0.83
Median	1	1
Range	0–4	0.3

*Data were not available for 3 out of 87 episodes

Table 3 Comparison of scores on the multidimensional scales in groups whilst on high-dose (HD) and low-dose (LD) prednisolone

Multifunctioning scales	HD group[a] Total score (mean)	LD group[a] Total score (mean)
Physical	966.7 (64.4)	1,223.3 (152.9)
Emotional	1,135 (75.7)	1,310 (163.7)
Social	675 (45)	1,065 (71)
School	1,035.3 (69.0)	1,275 (85)

[a] $n = 15$

agents that may have had an impact on relapse rate. Five patients were treated with rituximab around the time of relapse and had no further relapses in the following 6 months. Although a paired *t* test comparison did not quite reach statistical significance with a *p* value of 0.08, the numbers were very small and this is an interesting observation that requires further research. Ten of the patients were given a course of cyclophosphamide during the data collection period and in these patients there was a significant reduction in the number of relapses (*p* value =0.006).

There was a concern that treating with this new protocol may result in an increase in relapse rate. This was not shown to be the case. Although it can be argued that some patients may have gone into spontaneous remission, the definition of relapse remains the same and these patients were spared treatment with higher prednisolone doses.

We can postulate from this small study that larger doses of prednisolone may not be required in the treatment of relapses in all children with SSNS. In a selective cohort of cases, a lower-dose regimen can be effective in treating a relapse without compromising subsequent relapse rates.

These results are very encouraging, especially in relation to patient and parental concerns regarding the side effects associated with long-term treatment with high doses of prednisolone. Few studies have previously looked at the impact of the prolonged relapsing and remitting course of NS on the QoL and behavioural pattern of children [5, 7, 8]. Similarly, a small number of studies have looked at the detrimental effect of NS on families and caregivers [16–18]. A recent study by Mishra et al. [19] used the PedsQL Family Impact Module to show an impaired QoL amongst parents of children with NS; significantly higher scores were recorded amongst matched healthy controls in each of the categories and individual domains.

All these studies conclude that high-dose prednisolone therapy during a relapse adversely affects the QoL of children with NS and their parents. Our study is the first to show that the effects on QoL are significantly improved during treatment of a relapse with low-dose prednisolone therapy. The study showed significantly higher scores during treatment with low-dose prednisolone in each of the categories leading to a higher Total Health Summary Score. This difference persisted in the individual multifunctioning scales and was consistent within age groups. Although the difference in scores in all categories reached statistical significance, they were more marked in the Psychological Health Summary Score ($p = 0.0002$) than in the Physical Health Summary Score ($p = 0.001$). This supports previously reported data on the consequences of high-dose prednisolone therapy on behaviour in children. In the physical domain, scores relating to pain and energy levels were noted to be lower on high-dose therapy, thereby indicating a lower quality of life. Overall, these results would encourage a higher compliance rate in treating a relapse with low-dose prednisolone.

Interestingly, one of the parents completing the questionnaire recorded higher scores (i.e. a better quality of life) on treatment with high-dose prednisolone compared with low-dose treatment. Scores were higher in each individual domain, resulting in higher total scores. On reviewing the data, it was noted that this questionnaire had been completed with the help of an interpreter. One explanation could be that the parent had misunderstood the information conveyed to them regarding the filling in of the questionnaire.

Our study had some limitations, one being that it was a retrospective case note review. The study recruited as many patients as possible within a fixed time-scale. Sample size calculations were therefore done retrospectively with the expected proportion estimated to be 0.7 based on anecdotal experience. With these figures, the precision of the estimated proportion was calculated at 0.10, which resulted in a relatively wide 95 % CI at 0.60–0.79. The number of patients recruited for the second part of the study looking at the side-effects profile was small, but showed significant results. A part of the questionnaire was completed retrospectively and relied on parent memory; thus there was some potential for bias.

This study is important, as the role of low-dose prednisolone in treating a relapse of SSNS has not previously been

Table 4 Comparison of means (and SD) between different scores in groups whilst on high-dose (HD) and low-dose (LD) prednisolone

Categories	HD group[a]	LD group[a]	*p* value (95 % CI)[b]
Total health score	64.7 (14.56)	81.7 (13.76)	0.0002 (6.75–27.33)
Physical health summary score	69.0 (19.46)	85 (18.87)	0.001 (1.65–30.31)
Psychological health summary score	62.1 (14.52)	79.9 (11.95)	0.0002 (7.89–27.78)

[a] $n = 15$

[b] 95 % confidence interval of difference between two means

documented in the literature. Seventy percent of relapses treated with this regimen achieved remission, without compromising the relapse rate. We would conclude that in view of the improved QoL, a large randomised controlled trial is required, looking at the efficacy of the low-dose regimen versus the default regimen based on the original ISKDC protocol, even though recruitment to the trial may prove to be difficult.

Compliance with ethical standards

Conflicts of interest The authors declare they have no conflicts of interest.

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