

Chapter 14: Growth in Children with Established Renal Failure – a Registry Analysis

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Summary

- Short stature is a major problem in paediatric ERF patients with 29% of transplant patients and 41% of dialysis patients below the 2nd percentile for height.
- Only 6.5% of transplant patients and 15.5% of dialysis patients are receiving rhGH.
- There is no significant difference in the height distribution of patients commencing RRT and those who have had a functioning allograft for at least one year.
- In patients with at least 2 years between presentation and RRT, there is a significant fall in height Z score. This overall statistic is strongly influenced by the very poor growth of patients with glomerular disease.

Introduction

Achieving reasonable growth in children with chronic kidney disease and particularly those with ERF remains one of the greatest challenges for the paediatric nephrologist. Even with control of acidosis, electrolyte balance, renal osteodystrophy and supplemental nutrition, many children grow poorly and this is a major problem to the patients and their families. The recent Cochrane review¹ suggested that the use of recombinant human growth hormone (rhGH) was effective for patients regardless of their pubertal or treatment status. Since the initial studies of rhGH in patients with CKD in the early 1990s it has been licensed for use in the UK for over 10 years and certainly for the whole period the paediatric registry has been collecting data. In a recent review Mahan and Warady² found that there was reluctance amongst US paediatric nephrologists to use rhGH. They set out an algorithm, developed by members of a consensus committee, for the use of rhGH. In the light of this it

seemed important to examine the UK practice through the data available in the paediatric registry.

Analysis

The Registry collects anthropometric data at presentation, ERF commencement and annually thereafter. For the follow up records a note is also made as to whether rhGH has been used over the previous year. Data on rhGH usage over the past 5 years in patients where a complete data set is available is shown in Table 14.1. These data are divided according to whether patients had a functioning allograft or were on dialysis. In the dialysis population just 15.9% of patients on average, are receiving rhGH. These data show that there is certainly no upward trend in rhGH usage and if anything, the trend is downward. For transplant patients the trend is towards increasing usage, but the proportion receiving rhGH is much less, averaging just 4.3%.

These findings would be expected in a patient population that was growing well with little consequent need for rhGH. However, cross-sectional analysis shows this not to be the case. The cumulative frequency distribution of height in 273 patients with a functioning allograft for at least one year in 2005 and between the ages of 2 and 16 years at the time is shown with the data from 105 dialysis patients in that same age range in Figure 14.1. Although the transplant patients are significantly taller than those on dialysis (Figure 14.2, $p = 0.004$), both groups are well below the normal range. For the transplant patients, 48% were below the 10th percentile with 39% being below the 5th percentile and 27% below the second percentile. The corresponding figures for dialysis patients were 61% below the 10th percentile, 54% below the 5th percentile and 44% below the 2nd percentile. Thus, based on this cross-sectional analysis, it appears that rhGH is being

Table 14.1: Usage of growth hormone in dialysis and transplant patients

Year	Transplant patients			Dialysis patients		
	Patients	No on GH	% on GH	Patients	No on GH	% on GH
2001	358	14	3.9	122	23	18.9
2002	501	16	3.2	159	28	17.6
2003	479	15	3.1	134	17	12.7
2004	481	22	4.6	168	25	14.9
2005	400	26	6.5	142	22	15.5
Average	444	19	4.3	145	23	15.9

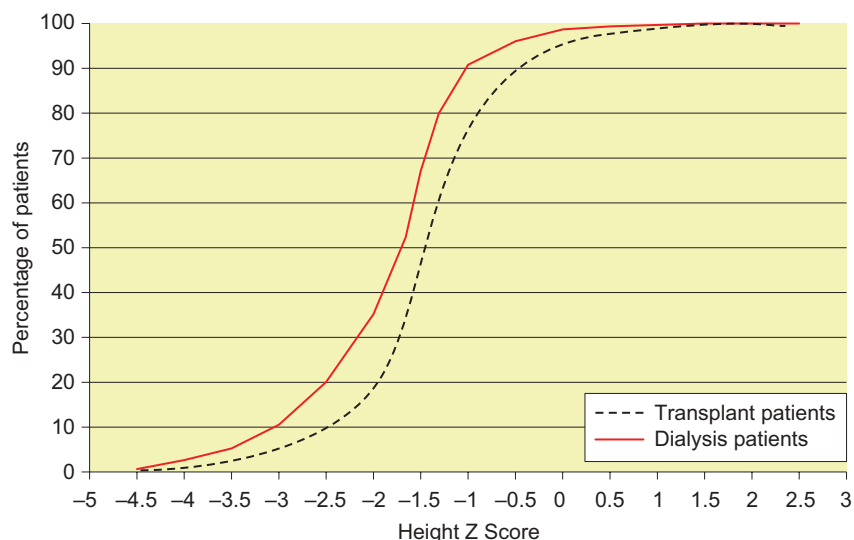


Figure 14.1: Height Z scores cumulative frequency distribution for ERF patients aged 2 to 16 years in 2005

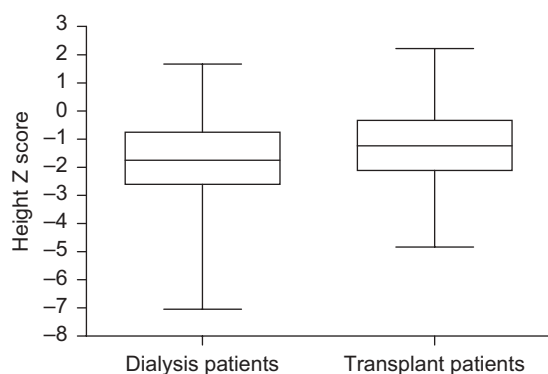


Figure 14.2: Height Z scores (median, quartiles, range) for ERF patients aged 2 to 16 years in 2005

under-used in the paediatric ERF population. This analysis was based upon those between the ages of 2 and 16 years of age as this is the group one would expect to potentially most benefit from rhGH. Analysis of all patients from the age of 2 to 20 years of age showed no difference and indeed, though the usage of rhGH was low, overall the frequency of usage was the same in those over the age of 16 as under the age of 16 years. The lower usage of

rhGH in transplant patients compared to dialysis patients could in part be secondary to the fear of rhGH stimulating the growth of renal cell carcinomas as described by Tyden *et al*³. However, wider analysis of these data available by Mehls *et al*.⁴ and the Cochrane review have suggested that this risk is low and should not prevent the usage of rhGH where indicated by growth parameters.

These data on height in the paediatric ERF population are clearly disappointing but not dissimilar to the findings of Mahan and Warady analysing the NAPRTCS dataset. Clearly the two most influential factors, after control of biochemical and nutritional status, are growth after transplantation and before commencing RRT as for the majority of paediatric patients, the longest periods of treatment are either conservative before RRT or with a functioning allograft. At present, the Registry does not collect data on pre-ERF CKD patients but analyses of data at presentation to nephrology services together with data

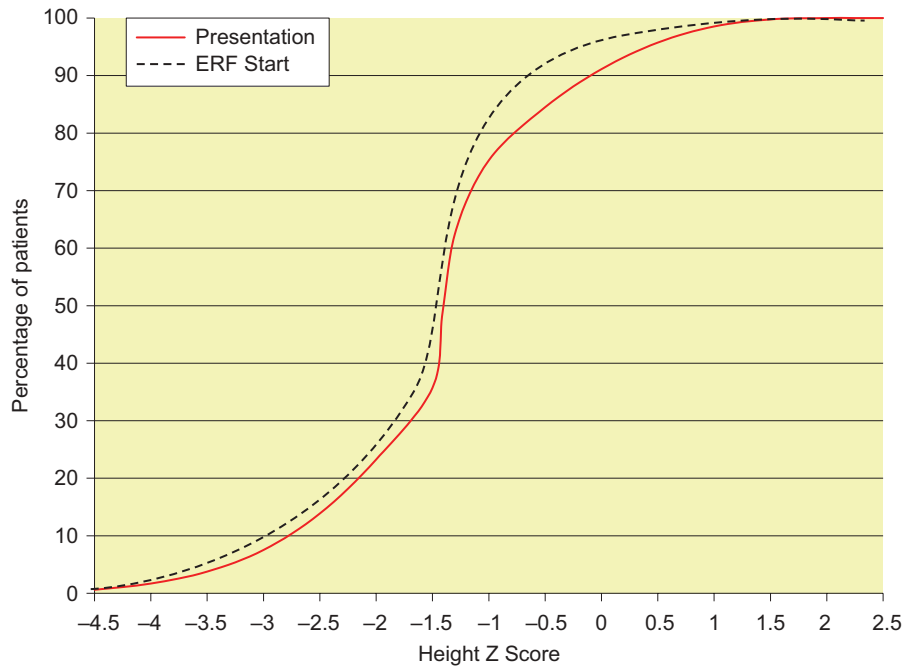


Figure 14.3: Height Z scores cumulative frequency distribution for patients at presentation and ERF commencement

at ERF commencement gives some insight into the CKD phase.

For this analysis 236 patients with complete anthropometric data, presenting between 2 and 16 years of age between 1996 and 2005, who had a minimum of two years between presentation and commencement of ERF were selected. These selection criteria allowed study of a population who had a reasonable period of time in the paediatric CKD clinic and for whom all interventions, including the use of rhGH would have been available. The height distribution of this population at presentation to nephrology services and at ERF commencement is shown in Figure 14.3. The population is clearly significantly smaller than normal with 50% being below the 10th percentile, 42% below the 5th percentile and 33% below the 2nd percentile at presentation. Overall, by the time these children entered ERF their height Z score had fallen rather than risen with 53% being below the 10th percentile, 45% below the 5th percentile and 34% below the 2nd percentile ($p = 0.0015$, Figure 14.4).

There are numerous factors that could affect growth in children with chronic kidney disease. One powerful factor is underlying diagnosis. Some conditions are associated with biochemical disequilibrium that is difficult to control or

are likely to be treated with steroid containing immunosuppressive regimes that will impair growth. Others, like nephropathic cystinosis, have been shown to respond well to rhGH in all phases of CKD management⁵. The series of figures below, show the change in height Z score from presentation to ERF commencement and the distribution of height Z scores at these two points in the main diagnostic groups. For patients with renal dysplasia, obstructive uropathy, reflux nephropathy and tubulo-interstitial disease (Figures 14.5 to 14.8), there is no significant difference in height Z score from presentation to ERF commencement. Tubulo-interstitial disease is in fact the only one of these four diagnostic groups where the

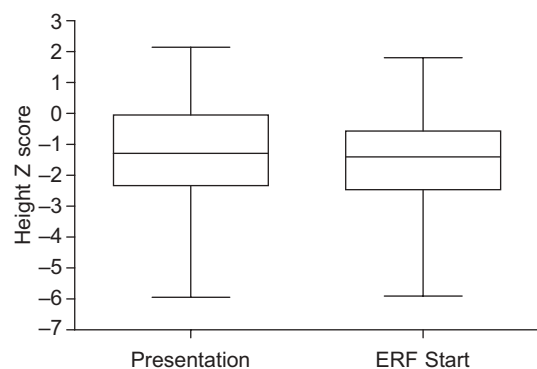


Figure 14.4: Median, quartiles and range of height Z scores for patients at presentation and ERF commencement

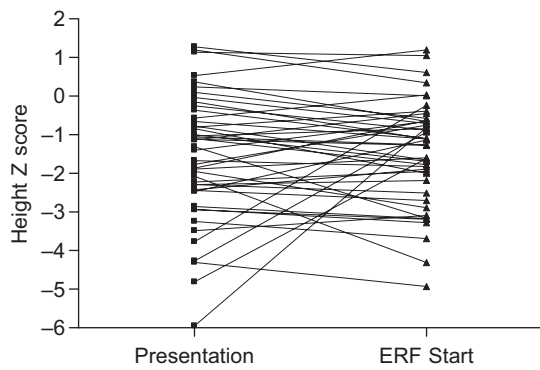


Figure 14.5a: Change in height Z score from presentation to ERF commencement in patients with renal dysplasia

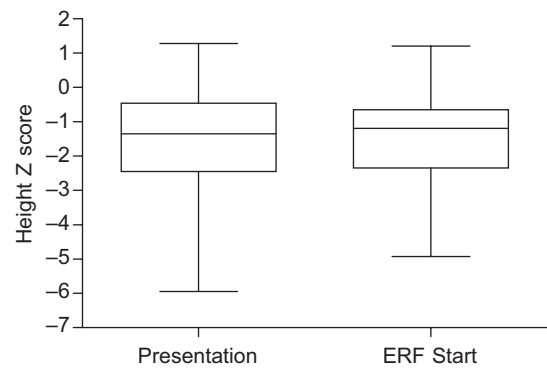


Figure 14.5b: Distribution of height Z score from presentation to ERF commencement in patients with renal dysplasia

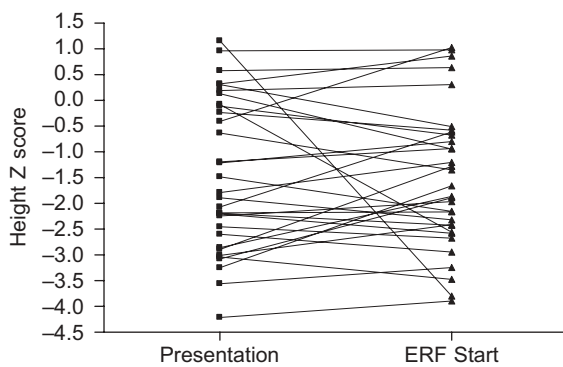


Figure 14.6a: Change in height Z score from presentation to ERF commencement in patients with obstructive uropathy

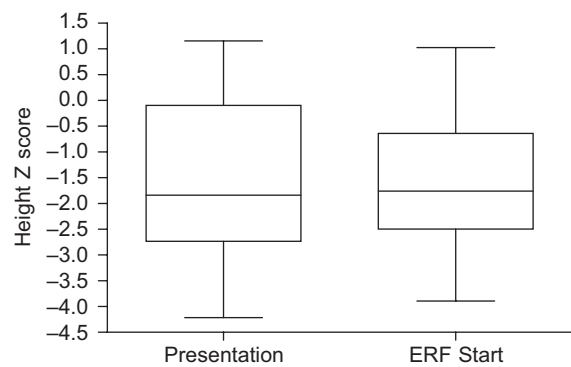


Figure 14.6b: Distribution of height Z score at presentation and ERF commencement in patients with obstructive uropathy

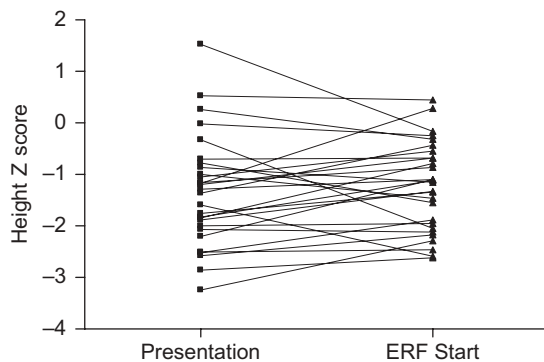


Figure 14.7a: Change in height Z score from presentation to ERF commencement in patients with reflux nephropathy

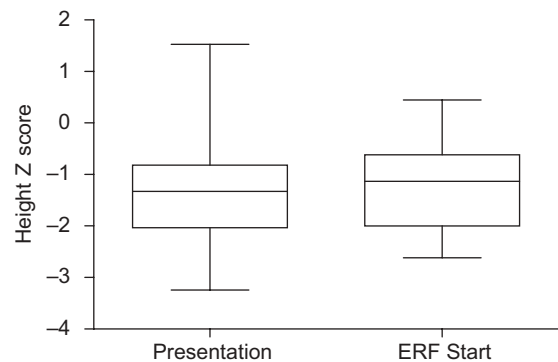


Figure 14.7b: Distribution of height Z score at presentation and ERF commencement in patients with reflux nephropathy

median height Z score at presentation is higher than at ERF commencement. For the large number of patients with glomerular disorders however, there is a significant fall in height Z score from presentation to ERF commencement ($p < 0.0001$, Figure 4.9).

The data for the 20 patients who had metabolic disease as a cause of ERF are shown

below in Figure 14.10. All these patients had cystinosis as the cause of their renal failure. Despite the data from Wuhl *et al.*⁵ suggesting that patients with cystinosis grow well with rhGH, there is no significant difference in the height Z score of these patients from presentation to ERF. To check that this was not just secondary to the small numbers of patients studied, the selection criteria rules were relaxed

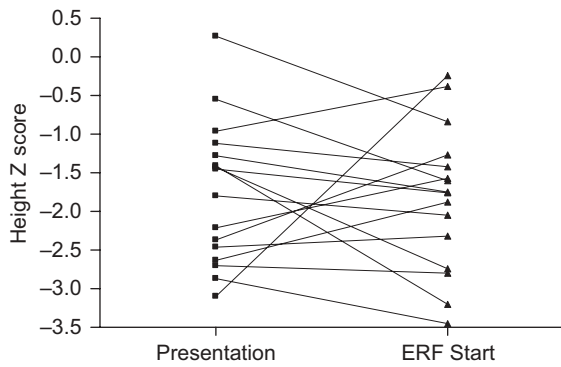


Figure 14.8a: Change in height Z score from presentation to ERF commencement in patients with tubulo-interstitial disease

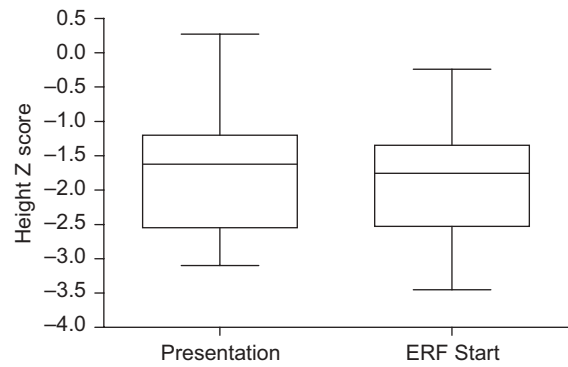


Figure 14.8b: Distribution of height Z score at presentation and ERF commencement in patients with tubulo-interstitial disease

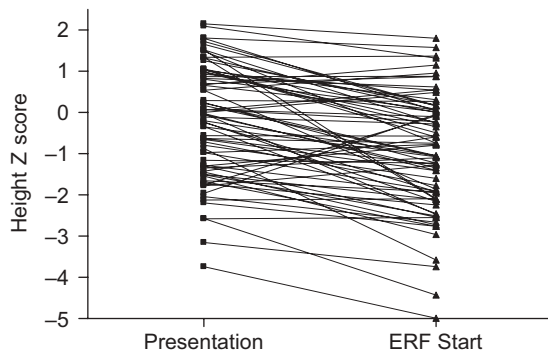


Figure 14.9a: Change in height Z score from presentation to ERF commencement in patients with glomerular disease

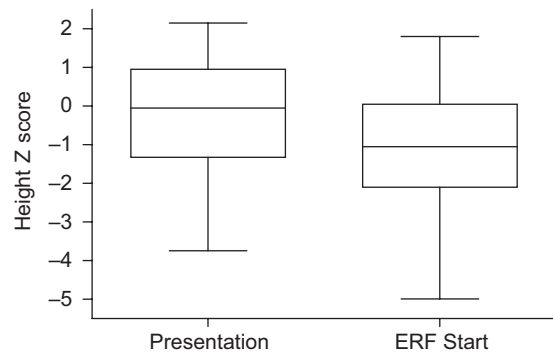


Figure 14.9b: Distribution of height Z score at presentation and ERF commencement in patients with glomerular disease

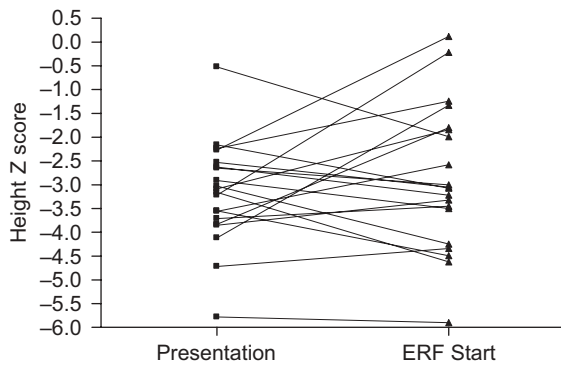


Figure 14.10a: Change in height Z score from presentation to ERF commencement in patients with cystinosis

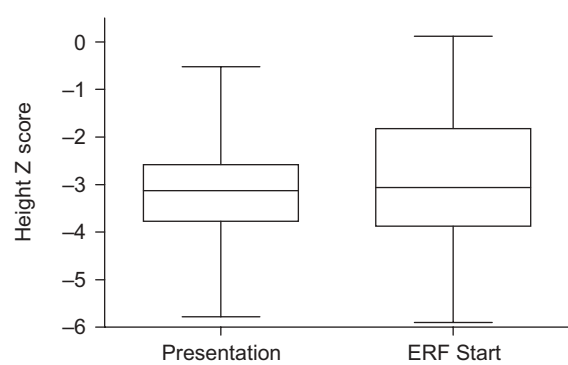


Figure 14.10b: Distribution of height Z score at presentation and ERF commencement in patients with cystinosis

to allow inclusion of patients presenting below the age of two years. This allowed the patient group to be almost doubled to 37. The result however, was identical. It is clear that whilst some patients are doing very well, others do badly. Unfortunately, no data are available on the detailed management of these patients so it is not possible to determine whether this is simply because some patients are not being offered

rhGH or whether there were other factors leading to poor growth in many of the patients.

Comparing the height distribution of the cohort of patients studied above when they start ERF management with the height distribution of the patients studied who were at least 1 year post transplant, there is no significant difference (Figure 14.11).

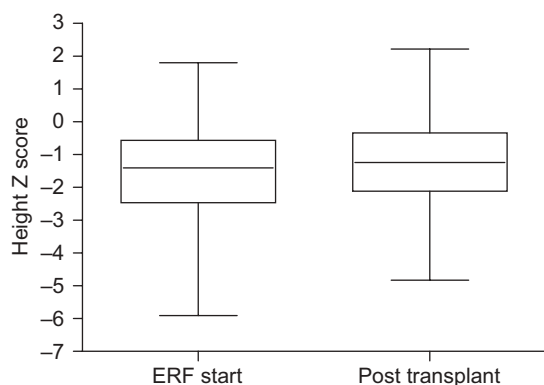


Figure 14.11: Height Z score at ERF start and at least 1 year post transplantation

Conclusions

Clearly, there are many factors that cannot be studied with the data available from the Registry dataset. However, it seems clear that growth in children with ERF is suboptimal. Growth acceleration is not being achieved in either the pre-ERF stage or after transplantation. Patients on dialysis are poorly grown. One factor that may be contributing to this is the relatively infrequent use of rhGH. Other factors that need to be considered are the control of acidosis, renal osteodystrophy and nutrition. Finally it is important to tease out the role of corticosteroids, both in patients post transplant and pre ERF patients with glomerulonephritis. Further studies using specific data collections

from a Registry cohort would be valuable in this regard.

References

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This report was reviewed, revised and approved by the Paediatric Renal Registry subcommittee comprising:

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