

Original articles**United Kingdom multicentre clinical trial of somatrem**

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SUMMARY In a multicentre clinical trial 54 children aged 4.0 to 17.3 years, who had growth hormone deficiency that had not previously been treated, were given biosynthetic methionyl growth hormone (somatrem) 4 units three times a week by subcutaneous or intramuscular injection for one year. Height was measured every three months for at least one year before and during treatment. Forty two patients responded to treatment with an increase in growth of >1.5 cm/year. The remaining 12 who grew more slowly were less obviously short and had a higher pretreatment growth than those who responded. The three who responded and the one who did not had undergone therapeutic spinal irradiation before starting the drug. If a whole year's pretreatment growth rate of <5 cm/year had been used as a diagnostic criterion the prediction of those who responded would have slightly improved. About two thirds of the patients developed antibodies against growth hormone and *Escherichia coli* protein; these were, however, of low and fluctuating titre and binding capacity, and did not influence the response to treatment. No adverse side effects were encountered. We conclude that somatrem is a safe and effective alternative to pituitary growth hormone.

The development of techniques for the large scale production of biosynthetic methionyl growth hormone (met-GH, somatrem) was welcomed, because of the limited availability of human pituitary glands from which growth hormone was extracted. Early batches of somatrem were contaminated with appreciable amounts of *Escherichia coli* protein,^{1 2} and it was not until 1984 that a multicentre trial of somatrem was possible in the United Kingdom. In May 1985 human pituitary growth hormone treatment was withdrawn and somatrem was granted a product licence later that year.³ This paper reports the results of a one year trial of somatrem, a preliminary account of which has already been published.⁴

Patients and methods**Children with growth hormone deficiency who**

Participating centres: Children's Hospital, Sheffield; Addenbrookes Hospital, Cambridge; General Infirmary, Leeds; Royal Belfast Hospital for Sick Children, Belfast; University Hospital of Wales, Cardiff; Queen's Medical Centre, Nottingham; Royal Victoria Infirmary, Newcastle upon Tyne; St Mary's Hospital, Manchester; The Children's Hospital, Birmingham; Royal Hospital for Sick Children, Bristol; St Bartholomew's Hospital, London; Alder Hey Children's Hospital, Liverpool; Leicester General Hospital, Leicester.

fulfilled the criteria of the Health Services Human Growth Hormone Committee⁵ were eligible for the trial, which entailed treatment with somatrem (Somatonorm, KabiVitrum, Stockholm, batches 81491, 89682, 53809, and 57091) 4 units three times a week by subcutaneous or intramuscular injection. Patients had not been previously treated with growth hormone, but all had been monitored for their growth rate for one year or more. The trial protocol was approved by the local ethical committee at each participating centre and consent was obtained from the parents in each case.

Patients were seen at three monthly intervals when height, both standing and sitting, was measured by standard techniques and samples of blood and urine were collected. Urine was tested for the presence of protein, blood, and glucose using dipstick methods. Blood was analysed at each centre for haematocrit, white cell count and differential, haemoglobin, blood glucose, serum albumin, urea, and creatinine concentrations; and alkaline phosphatase, glutamic oxaloacetic transaminase, and glutamic pyruvic transaminase activities by standard laboratory methods. Serum was stored on each occasion at -20°C and titres of antibodies to growth hormone measured by radioimmunoassay,⁶ and to *E. coli* protein by an enzyme linked immunosorbent

assay.⁷ The titre of antibodies to growth hormone was expressed as the logarithm of the serum dilution which bound 50% of a tracer amount of growth hormone labelled with I^{125} in a radioimmunoassay—for example, 50% binding at a serum dilution of 1/100 was expressed as a titre of 2.0. The titre of antibodies to *E. coli* protein was similarly expressed. The binding capacity of antibodies to growth hormone was calculated from Scatchard plot analysis and expressed as mg/l. X-ray pictures were taken for the determination of bone age by the TW2 method before treatment, and six and 12 months later. Not all laboratory and radiological measurements were made for each child on every occasion.

Between October 1984 and July 1985, 63 children were enrolled in the trial at 13 centres. Nine patients were subsequently omitted from analysis: two did not start treatment and seven stopped after three or six months. Table 1 gives a diagnostic classification of the 54 children treated with somatrem for one year. There were 33 boys and 21 girls, aged between 4.0 and 17.3 years at the start of treatment. Of the 11 patients in whom the cause of the hypopituitarism was known, nine had received either therapeutic or prophylactic cranial irradiation and two had craniopharyngiomas.

Patients were judged to have responded if the growth rate over one year of treatment increased 1.5 cm/year or more over the preceding year. Heights were converted into standard deviation scores by reference to published tables.⁸ Comparisons of growth rates between different subgroups and the possible effects of somatrem on laboratory measurements were analysed by Student's *t* test or non-parametric methods, as appropriate.

Results

Clinical. Forty two of the 54 patients responded to treatment with a satisfactory increase of growth rate. Of those who did not, one had multiple idiopathic pituitary hormone deficiency, was in late

puberty, and had a low growth rate (1.80 cm/year) before treatment; this did not change after treatment. Nine of the other 11 had been diagnosed as having isolated idiopathic growth hormone deficiency but had pretreatment growth rates of 5.0 to 9.6 cm/year. Side effects due to somatrem were not seen in any patient. Twenty six episodes of intercurrent illness were reported in 20 patients. These varied from upper respiratory tract infections and undiagnosed abdominal pain to naevoid basal cell carcinoma of the neck and trunk (Gorlin's syndrome).

Growth. The heights of children with non-idiopathic growth hormone deficiency were less abnormal before treatment than those of children with idiopathic growth hormone deficiency, but the mean growth rate of all the diagnostic subgroups was similar both in the year before treatment and during treatment (Table 1). As there were no significant differences among the subgroups, the group is considered together in further analyses. The change in mean growth rate from 4.6 to 8.3 cm as a result of treatment with somatrem is potentially misleading, as the figures include patients who did not respond and patients who had previously undergone spinal irradiation and who responded to treatment mainly by lower segment growth. Subdividing the group shows that the mean (SD) height of those who responded was -3.25 (0.98) standard deviation score, whereas that of those who did not was -2.44 (1.06) standard deviation score. The growth rate of those who did not respond was greater before treatment than that of the responders (Figure). Only three of 12 who did not respond had a growth rate of ≤ 5 cm/year before treatment, and seven of 42 who did respond had a growth rate before treatment of more than 5 cm/year. This simple criterion thus identified correctly 44 of 54 (81%) of the patients.

The mean (SD) increase in growth rate in the 42 who responded was $+4.6$ (1.8) cm/year. One patient

Table 1 Mean (SD) height, growth rate, and diagnoses of children treated with somatrem

	No of children	Height before treatment (SDS)	Height after treatment (SDS)	Growth rate before treatment (cm/year)	Growth rate during treatment (cm/year)
Idiopathic:					
Isolated growth hormone deficiency (total)	31	-3.32 (1.10)	-2.58 (0.93)	5.1 (1.8)	9.0 (2.2)
Isolated growth hormone deficiency (partial)	5	-3.15 (0.78)	-2.72 (0.77)	3.6 (1.1)	7.7 (2.0)
Multiple hormone deficiency	7	-2.75 (0.80)	-2.04 (0.91)	3.8 (1.2)	7.6 (3.0)
Non-idiopathic:					
Isolated growth hormone deficiency	7	-2.68 (1.05)	-2.43 (1.11)	4.4 (2.3)	6.9 (2.0)
Multiple hormone deficiency	4	-2.29 (0.93)	-1.88 (0.95)	3.8 (1.8)	7.0 (1.5)
Total	54	-3.08 (1.05)	-2.45 (0.94)	4.6 (1.8)	8.3 (2.3)

SDS is standard deviation score.

who had received spinal irradiation failed to respond, and when the other three irradiated patients were omitted the mean (SD) increase in growth rate of the remaining 39 was +4.8 (1.8) cm/year. Growth in the upper and lower segments of the four children who had received spinal irradiation was: 1.2+5.3=6.5; 2.4+2.5=4.9; 3.7+5.9=9.6; and 1.7+2.0=3.7 cm/year, respectively. The mean (SD)

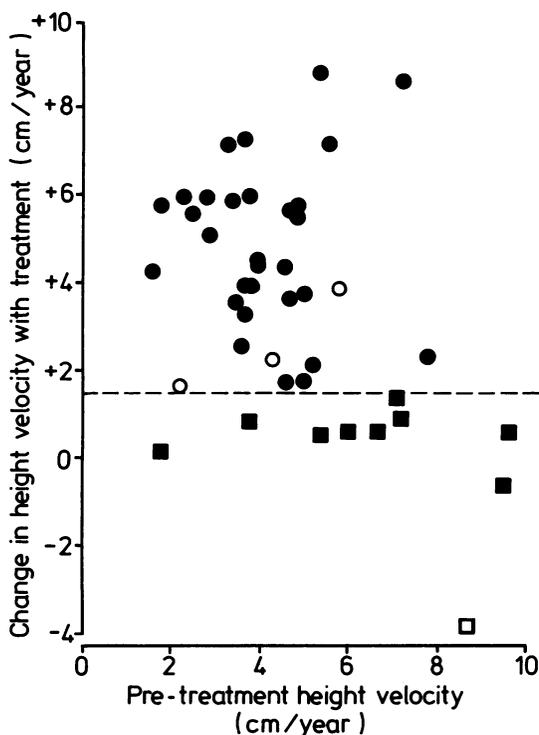


Figure Change in growth rate after treatment with somatrem for one year compared with that before treatment.

● = patients whose growth rate increased by >1.5 cm a year; ■ = patients who did not respond to somatrem; ○ = patients who underwent spinal irradiation.

Table 2 Presence of antibodies against growth hormone and *E coli* protein in children before and during treatment with somatrem

	Time (months)				
	0	3	6	9	12
Antibodies against growth hormone:					
No of patients	42	44	47	39	47
Percentage positive	0	57	70	72	64
Mean log titre (SD)	0	1.0 (0.9)	1.3 (1.0)	1.5 (1.1)	1.5 (1.3)
Maximum binding capacity (mg/l)	0	0.38	1.60	2.60	0.86
Antibodies against <i>E. coli</i> protein:					
No of patients	44	45	48	39	48
Percentage positive	39	56	87	79	69
Mean log titre (SD)	0.1 (0.2)	0.1 (0.2)	0.2 (0.2)	0.2 (0.2)	0.2 (0.2)

change in bone age during treatment was +1.23 (0.82) years (n=35). Six children who received their treatment by intramuscular injection had a mean (SD) growth rate of 8.4 (1.0) cm/year. This did not differ significantly from that of 32 who had their drug given by subcutaneous injection: 8.5 (0.4) cm/year.

Antibodies. Most children were tested for antibodies to growth hormone and *E. coli* protein at each visit (Table 2). Before somatrem treatment no antibodies to growth hormone were found, but 39% of children had antibodies to *E. coli* protein. As treatment progressed the number of children with antibodies to growth hormone rose; after six months it stabilised with about two thirds having antibodies. The percentage of children positive for *E. coli* protein also rose to a maximum of 87% at six months, but then declined to 67% at 12 months. The titre of growth hormone antibodies was low, the highest value being 3.8, and that of *E. coli* protein antibodies also low, the highest being 0.7. Only two sera from different patients had growth hormone binding capacities above 1 mg/l (Table 2), and in each case the value subsequently fell. Of the 175 sera examined between three and 12 months after the start of treatment, only 54 had detectable binding capacity (≥ 0.01 mg/l). There was no trend to increased binding capacity with length of treatment.

Growth rates were analysed after subdividing the children into those with a log titre of antibody to growth hormone of less than or greater than 1.1. The mean (SD) growth rate of 14 patients with a log antibody titre of less than 1.1 was 7.9 (0.8) cm/year, which did not differ significantly from that of 34 children with a titre of more than 1.1, 8.1 (0.3) cm/year. There was no correlation between binding capacity and growth rate. In particular, the patients who did not respond to somatrem had low or no binding capacity.

Laboratory tests. No clinically important change

occurred in the result of any haematological or biochemical test. Haematuria and glycosuria were not seen, but occasional slight proteinuria was recorded; this did not occur consistently in any patient.

Discussion

The United Kingdom multicentre clinical trial is the largest to evaluate somatrem using only one regimen. This permitted a critical assessment to be made of its antigenicity, as well as a careful analysis of the response to treatment in each diagnostic subgroup.

The somatrem used in the trial contained 2–4 ng *E. coli* protein per phial, appreciably less than earlier preparations.⁹ Although antibodies to growth hormone and *E. coli* protein developed in most patients, titres were low and fluctuated. More importantly, no patient developed a growth hormone antibody binding capacity (>7.5 mg/l) which could have inhibited the therapeutic effect.¹⁰

It is usual to report the results of treatment with growth hormone in terms of growth rate (cm/year), but this takes no account of the scatter of age, the potential for catch up (which is related to the duration of growth hormone deficiency), or the fact that some patients cannot respond fully because of previous spinal irradiation. For these reasons the results of this study were subdivided by diagnosis and by therapeutic response. The definition of response to treatment was based on the clinical experience of the Health Services Human Growth Hormone Committee. The cut off point, an increase in growth rate of more than 1.5 cm/year, was set deliberately low to avoid inappropriate exclusion.

Of the 12 who did not respond, nine came into the categories of idiopathic total or partial growth hormone deficiency, but had relatively high growth rates. This illustrates the poor diagnostic discrimination of biochemical tests. In contrast, the simple criterion of a whole year of growth rate before treatment of less than 5 cm/year would have predicted response marginally better. It was not possible to refine this predictor by conversion into standard deviation scores, as standards based on chronological age are inappropriate. As a group those who did not respond were less obviously short than those who did, but this information was of no help in sorting patients according to the aetiology of their growth hormone deficiency.

Examination of the diagnostic subgroups showed that patients with idiopathic growth hormone deficiency were shorter than those with overt hypothalamo-hypophyseal disease, presumably because other symptoms made the latter group seek medical attention earlier. There were no significant

differences among groups in response to somatrem treatment, and when those who did not respond and patients with spinal irradiation were excluded, the mean change in growth rate due to somatrem was similar to that seen in other trials despite differences in dose regimen.^{11 12} The use of a standard dose three times a week, irrespective of body size, ensured a uniform treatment protocol for all children. Response to treatment was not analysed by dose/kg body weight because, to make sense, the height velocity should be transformed into standard deviation score, and this was not possible.

The lack of adverse clinical or laboratory side effects was gratifying but not unexpected in the light of experience with earlier preparations of somatrem and pituitary growth hormone. We conclude from this study that somatrem is a safe effective alternative to human pituitary growth hormone for the treatment of children with growth hormone deficiency.

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