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Height Outcome of Recombinant Human Growth Hormone Treatment in Achondroplasia Children: A Meta-Analysis

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Key Words
Achondroplasia · FGFR3 · Height outcome · Growth hormone therapy · Meta-analysis · Skeletal dysplasia

Abstract
Background/Aims: Although recombinant human growth hormone (rhGH) is not approved to treat short stature of achondroplasia (ACH), some studies suggested growth improvement during short-term rhGH treatment. ***Methods:*** A meta-analysis of rhGH therapy efficacy in ACH children was performed. ***Results:*** From 12 English-language studies, 558 (54.0% males) rhGH-treated ACH children were enrolled. Administration of rhGH (median dosage 0.21 mg/kg/week; range 0.16–0.42 mg/kg/week) improved height (Ht) from baseline [–5.069 standard deviation score (SDS; 95% CI –5.109 to –5.029); $p < 0.0001$] to 12 [–4.325 SDS (95% CI –4.363 to –4.287); $p < 0.0001$] and 24 months [–4.073 SDS (95% CI –4.128 to –4.019); $p < 0.0001$]. Then, Ht remained approximately constant up to 5 years [–3.941 SDS (95% CI –4.671 to –3.212); $p < 0.0001$]. ***Conclusions:*** In ACH children, rhGH treatment increased Ht from –5.0 to –4.0 SDS during 5 years, but insufficient data are available on both the adult Ht and the changes of body proportions.

Introduction

Skeletal dysplasias often cause severe growth failure. Among them, achondroplasia (OMIM 100800; ACH) is the most common genetic form of chondrodysplasia in humans occurring in 1:15,000–1:40,000 live births [1, 2]. Since long bones, vertebrae and base of skull are affected, ACH is characterized by short-limbed marked short stature (rhizomelic dwarfism), relative macrocephaly with prominent forehead, midface hypoplasia, lumbar lordosis, trident configuration of hands and hydrocephalus during growth development caused by narrowing of the foramen magnum [2]. In addition to prepubertal growth failure, ACH children show decreased pubertal growth spurt [2].

Linear growth of patients with ACH is extremely impaired. Adult height (Ht) averages approximately 130 (118–145) cm and 120 (112–136) cm in untreated males and females [3], respectively, which is 6–7 standard deviations (SD) below the mean of the general population. This severe Ht deficit is largely due to shortened legs, while sitting height (SHt) is only 1–2 SD below the mean. Extremely short stature and disproportion cause considerable troubles in daily life and place considerable psychological pressure on the patients and their families.

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In 1994, the ACH locus was mapped to chromosome 4p16.3, and almost uniform (heterozygous and homozygous) mutations engaging the transmembrane region of the fibroblast growth factor receptor 3 (FGFR3) were identified shortly afterwards [1]. FGFR3 normally functions as inhibitor, acting negatively on both the proliferation and the terminal differentiation of growth plate chondrocytes [1, 2]. *FGFR3* mutations were subsequently discovered for other skeletal disorders such as thanatophoric dysplasia and hypochondroplasia [4, 5]. Today, ACH is part of a disorder spectrum caused by different mutations in the *FGFR3* gene, which includes more severe forms such as severe ACH with developmental delay and acanthosis nigricans, thanatophoric dysplasia [type I (OMIM 187601) and II (OMIM 187601)] and less severe forms such as hypochondroplasia (OMIM 146000) and even short subjects with normal body proportions [1, 6–8].

Surgical lengthening of the lower limbs has been performed to increase Ht and improve body proportion in ACH subjects, but this procedure requires long-term hospitalization and may result in serious complications, such as postoperative infections and fractures or deviations of the bone axis [9–11].

Trials with growth hormone (GH) treatment in ACH subjects have occurred for more than 50 years. In 1933, a therapeutic experiment was done using pituitary extracts in a patient with chondrodystrophy (presumably ACH) [11]. In 1985, synthetic recombinant human growth hormone (rhGH) became available, and it was possible to test its use in a wider range of conditions than simple replacement therapy for GH deficiency (GHD). Several trials explored rhGH treatment in ACH children, mostly using pharmacological doses comparable with those used in the Turner syndrome [12–19]. Early studies reported short-term (up to 2 years) treatment data on small groups of ACH patients [12, 19–22]. They suggested a modest increase in Ht velocity [15, 16, 18]. The relative growth velocity of lower versus upper body segments was not assessed in these trials. One uncontrolled intervention study reported on the long-term treatment (up to 6 years) of very young children (2.25 years old) suggesting significant benefits on Ht standard deviation score (SDS) [23]. In 2005, Hertel et al. [24] reported on 35 individuals, who gained an average of 1.0 SD in Ht SDS after 5 years of therapy.

Since no clear long-term benefit has been established, rhGH treatment for ACH is not approved by regulatory agencies in the USA and Europe. The aim of the present meta-analysis was to evaluate the long-term Ht outcome of rhGH treatment in ACH children in order to give a better indication for clinical practice in this rare disorder.

Methods

The report of this protocol-based review was consistent with the PRISMA statement (Preferred Reporting Items for Systematic Review and Meta-Analyses) such as Cochrane Organization Criteria [25, 26].

A computerized literature search using MEDLINE (PubMed) was conducted to identify previously published articles on the rhGH treatment of patients with ACH throughout December 31, 2015. The used keywords were growth hormone, growth, ACH, skeletal dysplasia, somatotropin, somatropin, rhizomelic stature, *FGFR3* gene functions, AND, and OR during searches. We also screened the reference list of all published original articles and several review articles were found for additional references.

Two investigators independently examined the published manuscripts for possible overlapping data and any discrepancies were resolved by consensus. Eligible studies were randomized controlled trials or not, published in any language, which were allocated to either rhGH treatment or no active treatment. Finally, only English full-text articles were included.

Two reviewers independently completed data extraction forms on each trial. These included data on the trial design, quality and outcomes. Where trial eligibility or methodological aspects were uncertain, the authors were contacted for clarification. For cross-over trials, only data from the first phase of the study were included. For parallel studies, data were included up to the end of the randomized phase only. Calculations were performed by one investigator and checked by another. Discrepancies between the investigators were discussed and resolved by agreement.

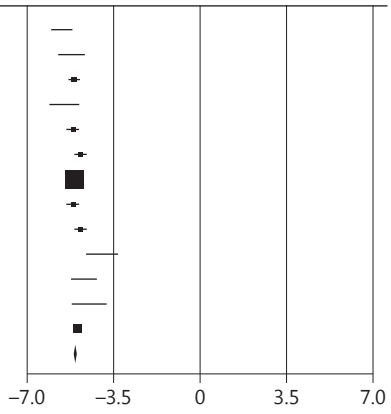
Publication bias and heterogeneity were evaluated with Begg-Mazumdar's test and I^2 [25]. The power with reference to the significant differences was >0.8, assuring an appropriate sample size in the meta-analysis.

The meta-analysis was performed considering sample sizes, standard errors and differences in means of continuous outcomes. Data were calculated with the Comprehensive Meta-Analysis V2 software and summarized in the following forest plots, as previously used [27–29].

Results

Of the eligible articles, 34 English-language reports evaluated linear growth outcomes of ACH children using rhGH treatments [12–24, 30–50]. Nine reports [16, 17, 37–43] were excluded from our analysis, because they used pituitary-extracted human GH. Three reports [44, 45, 50] were excluded from our analysis because the statistical software that was used required at least 2 patients for each group (i.e. study protocol). Two studies [18, 19] were excluded because they expressed Ht values as ACH SDS. One study [46] was excluded because rhGH treatment duration was less than 12 months. Since only clinical data (i.e. Ht, SHt) expressed as arithmetic mean and SD could be meta-analyzed, 12 studies [12–15, 21–24, 30,

First author [Ref.], year	Statistics for each study							Mean and 95% CI
	mean	standard error	variance	lower limit	upper limit	Z-value	p value	
Hertel [24], 2005	–5.600	0.212	0.045	–6.016	–5.184	–26.399	0.000	
Hertel [24], 2005	–5.200	0.267	0.071	–5.723	–4.677	–19.491	0.000	
Kanazawa [22], 2003	–5.100	0.117	0.014	–5.329	–4.871	–43.574	0.000	
Tanaka [31], 2003	–5.500	0.302	0.091	–6.091	–4.909	–18.241	0.000	
Seino [13], 2000	–5.150	0.130	0.017	–5.404	–4.896	–39.727	0.000	
Seino [13], 2000	–4.830	0.121	0.015	–5.066	–4.594	–40.066	0.000	
Ramaswami [23], 1999	–5.100	0.024	0.001	–5.148	–5.052	–209.528	0.000	
Seino [47], 1999	–5.150	0.130	0.017	–5.404	–4.896	–39.727	0.000	
Seino [47], 1999	–4.830	0.121	0.015	–5.066	–4.594	–40.066	0.000	
Stamoyannou [12], 1997	–3.980	0.325	0.105	–4.616	–3.344	–12.263	0.000	
Hagenäs [30], 1996	–4.700	0.260	0.068	–5.209	–4.191	–18.090	0.000	
Hagenäs [30], 1996	–4.500	0.348	0.121	–5.182	–3.818	–12.937	0.000	
Bridges [21], 1994	–4.970	0.058	0.003	–5.083	–4.857	–86.100	0.000	
	–5.069	0.020	0.000	–5.109	–5.029	–248.188	0.000	



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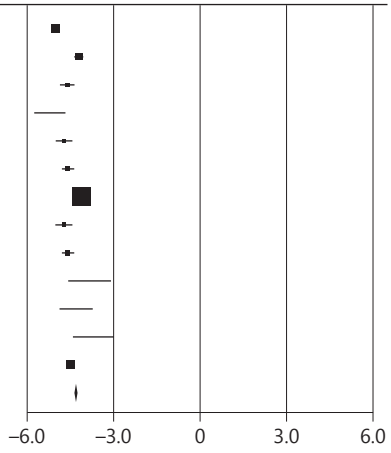
First author [Ref.], year	Statistics for each study							Mean and 95% CI
	mean	standard error	variance	lower limit	upper limit	Z-value	p value	
Hertel [24], 2005	–5.000	0.058	0.003	–5.113	–4.887	–86.957	0.000	
Hertel [24], 2005	–4.200	0.072	0.005	–4.342	–4.058	–58.095	0.000	
Kanazawa [22], 2003	–4.600	0.117	0.014	–4.829	–4.371	–39.302	0.000	
Tanaka [31], 2003	–5.200	0.271	0.074	–5.732	–4.668	–19.163	0.000	
Seino [13], 2000	–4.720	0.143	0.020	–4.999	–4.441	–33.100	0.000	
Seino [13], 2000	–4.570	0.105	0.011	–4.776	–4.364	–43.385	0.000	
Ramaswami [23], 1999	–4.100	0.026	0.001	–4.151	–4.049	–157.506	0.000	
Seino [47], 1999	–4.720	0.143	0.020	–4.999	–4.441	–33.100	0.000	
Seino [47], 1999	–4.570	0.105	0.011	–4.776	–4.364	–43.385	0.000	
Stamoyannou [12], 1997	–3.820	0.374	0.140	–4.553	–3.087	–10.210	0.000	
Hagenäs [30], 1996	–4.300	0.289	0.083	–4.866	–3.734	–14.896	0.000	
Hagenäs [30], 1996	–3.700	0.348	0.121	–4.382	–3.018	–10.637	0.000	
Bridges [21], 1994	–4.480	0.058	0.003	–4.593	–4.367	–77.611	0.000	
	–4.325	0.019	0.000	–4.363	–4.287	–223.170	0.000	



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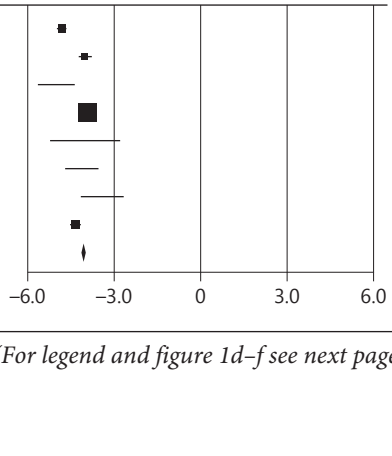
First author [Ref.], year	Statistics for each study							Mean and 95% CI
	mean	standard error	variance	lower limit	upper limit	Z-value	p value	
Hertel [24], 2005	–4.800	0.078	0.006	–4.953	–4.647	–61.584	0.000	
Hertel [24], 2005	–4.000	0.109	0.012	–4.213	–3.787	–36.851	0.000	
Tanaka [31], 2003	–5.000	0.316	0.100	–5.620	–4.380	–15.811	0.000	
Ramaswami [23], 1999	–3.900	0.034	0.001	–3.966	–3.834	–115.800	0.000	
Stamoyannou [12], 1997	–3.990	0.615	0.378	–5.195	–2.785	–6.488	0.000	
Hagenäs [30], 1996	–4.100	0.289	0.083	–4.666	–3.534	–14.203	0.000	
Hagenäs [30], 1996	–3.400	0.379	0.144	–4.144	–2.656	–8.960	0.000	
Bridges [21], 1994	–4.330	0.086	0.007	–4.499	–4.161	–50.213	0.000	
	–4.073	0.028	0.001	–4.128	–4.019	–146.701	0.000	



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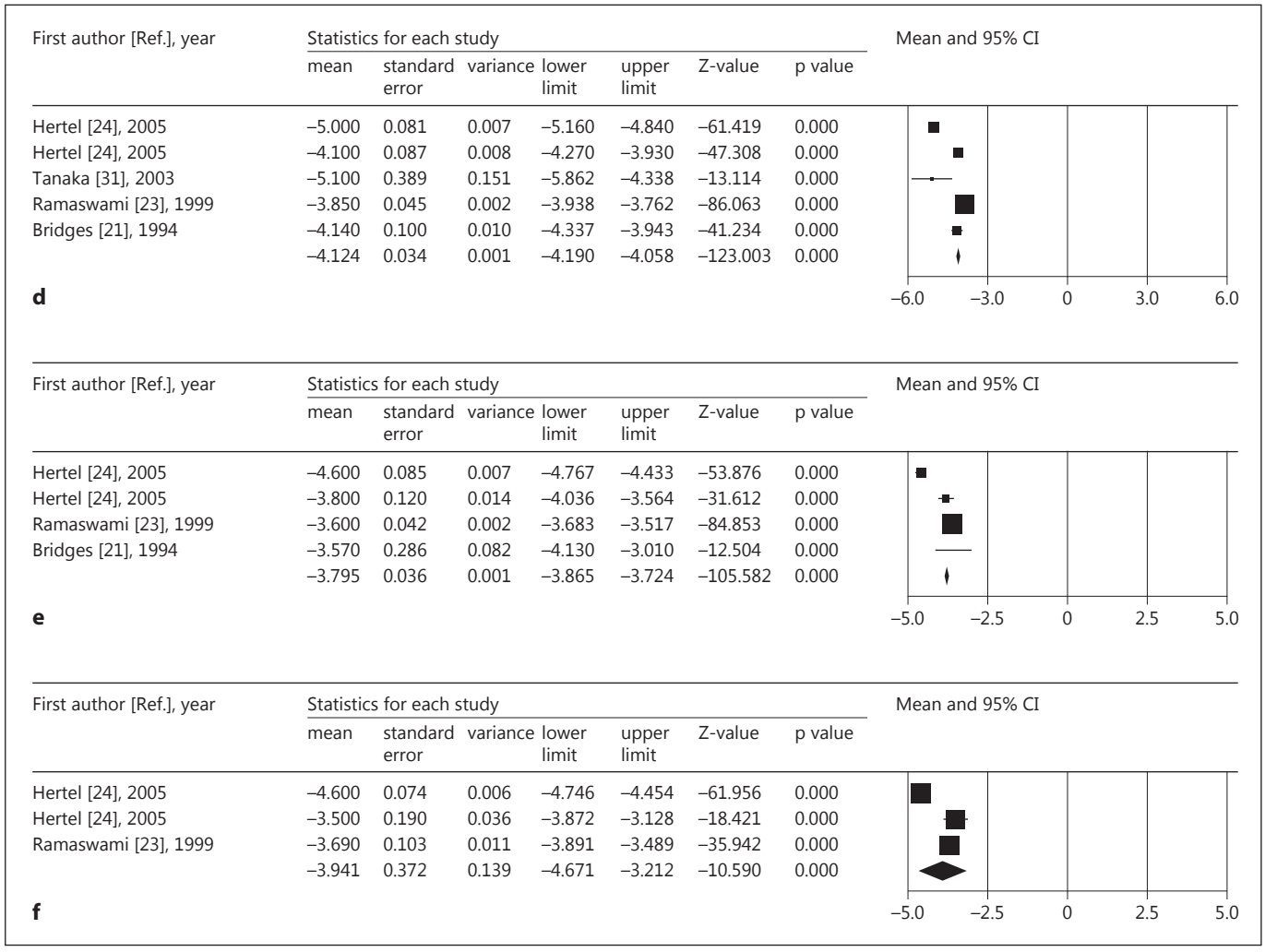

Fig. 1. Meta-analysis of Ht SDS at baseline and after 12, 24, 36, 48 and 60 months of rhGH treatment in patients with ACH. **a** Baseline. **b** After 12 months. **c** After 24 months. **d** After 36 months. **e** After 48 months. **f** After 60 months. Each included study is represented by one square while the square area is proportional to the sample size (i.e. patient amount). The horizontal lines represent the confidence intervals (95% CI) while the vertical lines crossing the zero value (i.e. the no-effect vertical line) mean the absence of a significant difference. If the study square or its horizontal line overlaps the no-effect vertical line, there is no statistical significance. The meta-analysis summary measure is reported at the bottom of the left side, corresponding to a diamond or small vertical bar. If the diamond does not cross the no-effect vertical line, the result of the meta-analysis is statistically significant. The values (difference in means, p values, confidence intervals, etc.) are indicated between the study names and the graphic.

31, 47, 48] were selected; one of these articles [47] also included genetic data.

From the 12 selected studies [12–15, 21–24, 30, 31, 47, 48], 558 rhGH-treated children with ACH were enrolled (n = 507; 54.0% males; 46.0% females). Due to cohort limitations and nonstandardized data, it was not possible to separately analyze rhGH-induced growth outcome of ACH subjects with or without GHD. Most of the enrolled patients were prepubertal or in early pubertal development at the start of rhGH treatment (median dosage 0.21 mg/kg/week; range 0.16–0.42 mg/kg/week).

In all ACH children evaluated (n = 498), mean Ht at rhGH therapy start was subnormal in each of the studies [–5.069 SDS (95% CI –5.109 to –5.029); $p < 0.0001$] (fig. 1a) [12, 13, 21–24, 30, 31, 47]. As shown in figure 1, Ht progressively increased during rhGH treatment, with major growth improvement at 12 months [n = 494; –4.325 SDS (95% CI –4.363 to –4.287); $p < 0.0001$] (fig. 1b).

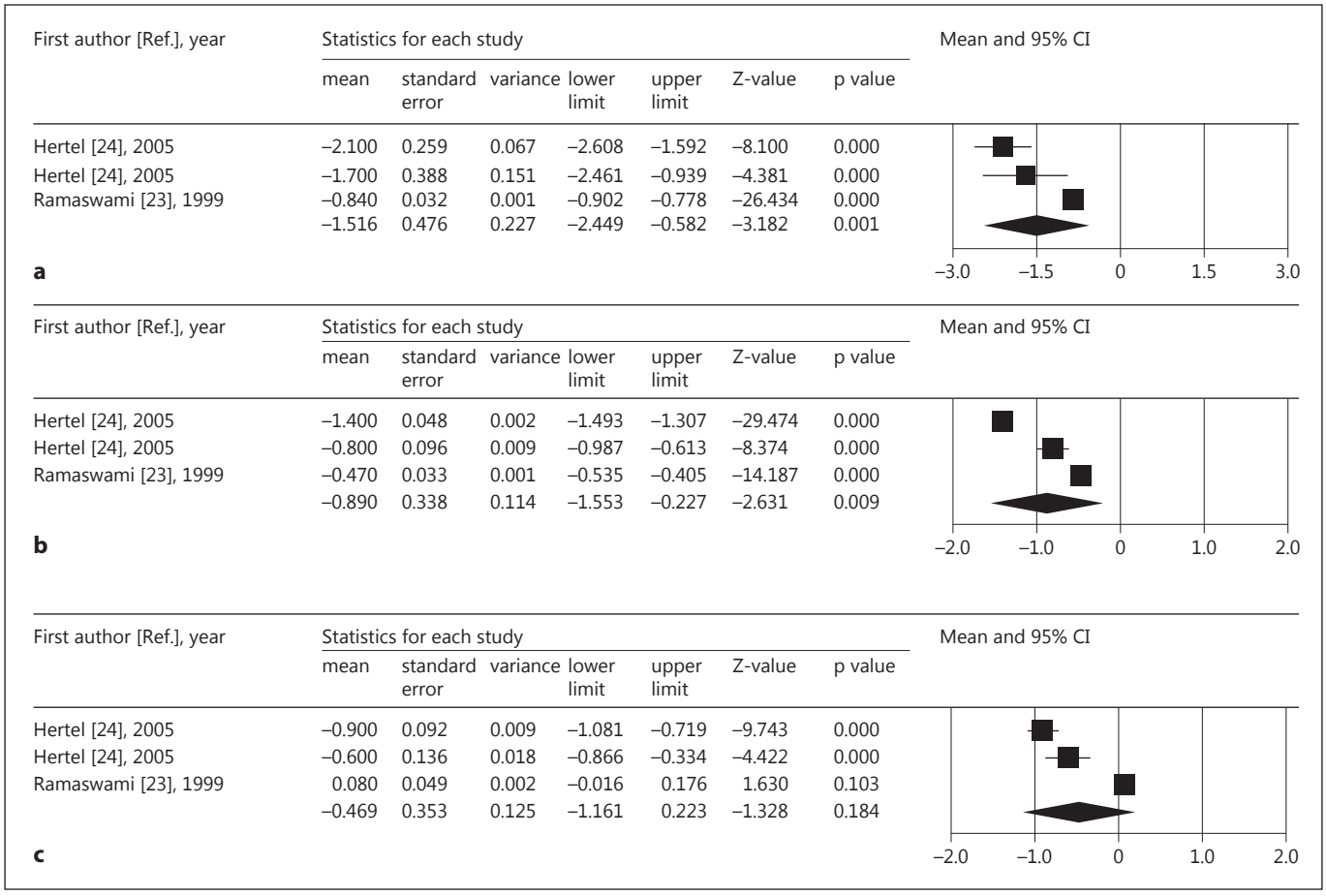

Fig. 2. Meta-analysis of SHt SDS at baseline and after 12 and 24 months of rhGH treatment in patients with ACH. **a** Baseline. **b** After 12 months. **c** After 24 months. Each included study is represented by one square while the square area is proportional to the sample size (i.e. patient amount). The horizontal lines represent the confidence intervals (95% CI) while the vertical lines crossing the zero value (i.e. the no-effect vertical line) mean the absence of a significant difference. If the study square or its horizontal line overlaps the no-effect vertical line, there is no statistical significance. The meta-analysis summary measure is reported at the bottom of the left side, corresponding to a diamond or small vertical bar. If the diamond does not cross the no-effect vertical line, the result of the meta-analysis is statistically significant. The values (difference in means, p values, confidence intervals, etc.) are indicated between the study names and the graphic.

Then, rhGH-induced Ht stabilized from 24 months [n = 102; –4.073 SDS (95% CI –4.128 to –4.019); $p < 0.0001$] (fig. 1c) until 5 years of rhGH treatment [n = 21; –3.941 SDS (95% CI –4.671 to –3.212); $p < 0.0001$] (fig. 1e, f). Only one study [23] reported Ht data for longer treatment than 5 years excluding additional meta-analysis.

At the start of rhGH therapy, SHt was significantly reduced [n = 70; –1.516 SDS (95% CI –2.449 to –0.582); $p = 0.001$] (fig. 2a): it reflected data from only two studies [23, 24]. During rhGH treatment, SHt progressively increased at 12 months [n = 66; –0.890 SDS (95% CI –1.553 to –0.227); $p < 0.05$] (fig. 2b), but was not statistically significant at 24 months [n = 50; –0.469 SDS (95% CI –1.161 to 0.223); $p > 0.05$] (fig. 2c) or later at 60 months (data not shown) for the few subjects included. No other correlations on the body proportions (i.e. subischial leg length SDS or SHt/Ht ratio SDS) were possible to include in the meta-analysis due to limited and nonstandardized published data.

Most studies reported that bone age progressed in parallel with chronological age during rhGH treatment, while rhGH-treated ACH children often presented slight pubertal delay (meta-analysis not performed) [12–15, 21–24, 30, 31, 47, 48]. No serious adverse events were reported during rhGH treatment [12–15, 21–24, 30, 31, 47, 48].

Discussion

Linear skeletal growth relies on enchondral ossification of the growth plate cartilage in which chondrocytes undergo a tissue-specific process of proliferation and maturation [1]. The pathogenesis in ACH is caused by defects in enchondral ossification resulting from a genetic mutation causing increased FGFR3 activity [2]. It is unknown why growth of the extremities, especially their proximal portions, is predominantly affected in contrast to the marginally affected growth of the trunk.

A progressive Ht deficit is the predominant phenotype observed in ACH patients. After the first year of life, the spontaneous growth rate is equivalent to the 3rd percentile of healthy children and remains at this low rate during all childhood, leading to extremely short adult stature [2]. The social disadvantages and psychological problems of severe growth impairment place pressure on the patients and their parents to seek growth-promoting strategies. Although a new promising treatment may become available in the future [51, 52], there are currently few therapeutic options for growth failure in ACH subjects.

Surgical limb lengthening is an effective approach to increase Ht in ACH [9, 10]. It involves breaking bones, usually femurs, tibiae, and humeri, followed by slow stretching during the healing process by means of orthopedic appliances, permitting increases of 15–30 cm to adult standing Ht [2]. Indeed, this procedure remains controversial because of the need of repeated surgeries, extended time that orthopedic appliances must be in place, superficial wound infections, and complications related to stretching of nonskeletal tissues including nerves and blood vessels [2, 9, 10]. Because these procedures are quite invasive and costly, rhGH therapy has been explored in ACH children. Some studies indicated that such treatment in children with ACH may prevent the accumulating Ht deficit by maintaining growth velocity near the normal range [13, 15, 23, 47]. The overall results indicated a 67–75% increase in growth velocity and a gain of 0.2–0.5 SDS, respectively, during the first year of treatment. However, growth velocity was quite low after the second year of treatment in comparison with that of children with GHD [13]. Few long-term reports exist, reporting a gain of about 1–1.2 SD over 5 years of treatment and individual responses were variable [23].

To the best of our knowledge, this is the first meta-analysis on the rhGH treatment in children with ACH. It was based on rigorous, systematic methods and meta-analysis; all published studies evaluating rhGH therapy in ACH patients have been identified and a sensitive search strategy permitted to analyze growth patterns of large number of patients (n = 558). As for other rare disorders [27–29], the use of meta-analysis better estimates the effect of rhGH treatment than single studies. Our data from 12 meta-analyzed studies showed a mean Ht gain of 0.744, 0.996, 0.945, 1.275 and 1.128 SDS after 12, 24, 36, 48 and 60 months, respectively. After Ht increase in the first 24 months, rhGH administration stabilized Ht outcome at about –4.0 SDS up to 5 years. However, adult Ht of rhGH-treated subjects with ACH could not be quantified, since only one study reported Ht data for treatment period longer than 5 years, which prevented further meta-analyses [23].

Several studies reported ambiguous data with regard to body disproportion in ACH subjects over the rhGH treatment period [23, 24]. Some authors showed that the relative SHt did not significantly change during the study period, but that the ratio of lower limb length to standing Ht significantly improved [12, 19, 22]. Seino et al. [20] confirmed that the lower-limb-to-height ratio significantly increased during rhGH treatment, indicating improved body proportions. Surprisingly, Shohat et al. [19] demonstrated an even greater growth acceleration of the more severely affected areas during 1 year of rhGH treatment, as indicated by increased growth rate of lower versus upper segment, and of arm span versus Ht, confirming that 1 year of rhGH treatment did not increase the body disproportion in ACH. In the present study, we could only meta-analyze SHt SDS due to limited and not standardized published data of other body proportions (e.g. subischial leg length SDS or SHt/Ht ratio SDS). Although improvement of SHt SDS was found, it was limited to the first year of rhGH treatment for few enrolled subjects. In addition, SHt SDS is not a proper indicator of body proportion, because other parameters (e.g. SHt/Ht ratio SDS) have to be taken into account for body proportion evaluation [53]. Therefore, the effect on body disproportion in ACH during rhGH treatment still needs to be established.

Most ACH patients suffer from hydrocephalus, probably due to a narrowing of the occipital foramen magnum of spinal stenosis [2], by possible negative effects on the endochondral ossification of the cranial base and upper cervical spine [14]. In theory, rhGH treatment could worsen such stenosis, but no evidence of spinal cord compression or narrowing of the foramen magnum and any acromegalic-like signs during rhGH treatment were reported in the papers that were analyzed.

Although the present meta-analysis suggests that rhGH treatment may improve growth pattern in children with ACH, more data are needed before a final conclusion can be reached. Present results were limited by the weaknesses

of some trials often including few patients. Other issues were poor reporting of study design, unavailability of raw data in many studies, failure to analyze by intention to treat, and possible inadequate concealment of allocation. Although examination of funnel plots suggested that a small-study effect was unlikely, subgroup analyses or meta-regression, using study level covariates, could not be performed because of the relatively small available samples.

In conclusion, this meta-analysis suggests that rhGH therapy may have some beneficial effects in the treatment of short stature of children with ACH over a period of 5 years. However, the effect on adult Ht and on body disproportion is still unknown, as well as possible effects of coadjuvant use of rhGH treatment with other treatment (e.g. limb surgical lengthening, CNP/NPR-B analogs, statins, etc.).

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Disclosure Statement

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the paper. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. No writing assistance was utilized in the production of the manuscript.

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