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Evaluation of rgGH Therapy in Treating Small Stature as a Result of Being Born Small for Gestational Age (SGA) Without Catch-up Growth

Ralph Ballard
The Latymer School, United Kingdom
ralph.ballard04@outlook.com

Abstract

Being born small for gestational age (SGA) refers to being born with a birth weight under two standard deviations for the gestational age and sex of the population. 10% of children born SGA will not experience catch-growth and, if left untreated, this can result in a lower health-related quality of life. Recombinant growth hormone (rhGH) therapy is a common treatment that aims to increase the height velocity of children suffering from short stature. Although many studies have been carried out into the use of rhGH in treating short stature, few have focused solely on its effect on children born SGA. This literature review analysed sources from three databases (n=634) and evaluated the safety, effectiveness and outcomes of rhGH therapy in treating children born SGA. The main conclusions reached were that SGA children usually react well to treatment with a +1.03 SDS change over the first two years, but that the overall outcome will be affected by a number of factors. The treatment was deemed cost-effective for the change in quality of life. Although most side effects were positive - including improved lipid profile, lean mass and Performal IQ - not enough data was present to come to a clear conclusion on metabolism, while the treatment led to an over-correction of insulin sensitivity resulting in subjects being at greater risk of Type 2 diabetes. There was a lack of data on long-term effects. Overall, it appears rhGH is effective in treating children of short stature born SGA without catch-up growth.

Keywords: SGA, rhGH, short stature

Introduction

Small for gestational age (SGA) refers to a child with a birth weight under two standard deviations for the gestational age and sex of the population (Jancevska et al., 2012). The range of factors for children being born SGA include, but are not limited to, maternal and paternal influences and also genetic factors or disorders. Globally, 16% of infants are born SGA (Campisi et al., 2019) and 10% of these do not experience catch up growth and remain two SDs below the average height for their age and sex. Children with SGA who have gone for more than four years without experiencing catch-up growth are often considered for growth hormone treatment. The prevalence in a general paediatric population of children born SGA who qualify for GH treatment was 1:3250 so this is a widespread issue (Tamaro et al., 2021).

Being born SGA has been associated with problems in health-related quality of life (HRQoL), behaviour and cognitive development. Studies such as that by Goedegebuure et al. (2018) have shown that subjects who additionally received GH treatment have a significantly higher quality of life regarding positive emotions.

Norditropin SimpleXx is a drug used to treat growth failure in children due to a variety of causes including growth hormone deficiency, Turner syndrome, Noonan syndrome, reduced kidney function and SGA. In adults it can be used

to maintain the correct balancing of hormones. The active ingredient in Norditropin SimpleXx is the biosynthetic human growth hormone somatropin. Somatropin is classified as recombinant human growth hormone (rhGH). rhGH differs from pituitary-derived human GH (hGH) in that it is produced artificially, but has the same amino acid sequence.

rhGH is a relatively new innovation in the pharmaceutical field. In 1981, the first rhGH was developed and trialled using recombinant DNA technology. In 1985, a link between human pituitary GH and Creutzfeldt-Jakob disease (a fatal degenerative brain disorder) was discovered and use of human pituitary GH ceased. By the 1990s, hGH had been replaced by recombinant growth hormone. There are currently many brands of rhGH, including Nutropin, Humatrope, Genotropin and Norditropin – all produced by different pharmaceutical companies. However, all contain somatropin and are similar in efficacy, composition and cost, with the only differences being related to their formulations and delivery devices. This literature review will be mostly focused on Norditropin but will include articles related to all brands of somatropin as they are virtually indistinguishable from one another.

Although there have been many studies into the effects of rhGH and its cost effectiveness, most have grouped SGA without catch-up growth in with other causes of short stature. This literature review focuses on the use of rhGH in treating those born SGA who did not experience catch-up growth. It will evaluate both the length and cost of the treatment and the potential results and improvement in health-related quality of life due to the height gain provided by the treatment. The literature review will seek to compile articles related to the possible side-effects of the treatment and these will also be considered when evaluating the overall use of the treatment.

Methodology

The literature review was conducted utilising three separate databases - PubMed, Google Scholar and MedRvix. To ensure the results were relevant to the study, two key search terms were used, and these were 'SGA' and 'Norditropin'. (Referring to the brand of rhGH commercially known as Norditropin SimplexX.) From these two search terms, 320 results were obtained from PubMed and 314 from Google Scholar. Using both search terms and 'Norditropin' on its own, no results were retrieved in MedRvix while using the search term 'SGA' alone returned 13 results. None of the MedRvix results were related to studies involving people born small for gestational age and treated with rhGH and so these could be discarded as irrelevant to the study.

In order to narrow down the 634 combined results from the PubMed and Google Scholar databases to those relevant to the topic, several exclusion criteria were applied. If any one of the following criteria were met, the article or paper was excluded from the literature review. Firstly, if the article was not solely focused on subjects receiving rhGH treatment due to short stature or GH deficiency caused by being born small for gestational age, the article was disregarded. This included articles where the focus was on other causes such as Noonan's syndrome and was done in order to prevent these other factors from influencing the results of the review. Next, the study was disregarded if it was not directly related to growth hormone treatment itself or if it was focused on growth hormone treatment for adults. This is because rhGH treatment is used for growth hormone replacement in adults, rather than growth failure as it is in children, and so does not treat the effects of growth hormone deficiency caused by being born SGA. Articles that were dated from before 2000 were disregarded as the use of rhGH has become more widespread since then. Articles focused on a geographical area outside Europe or North America were disregarded to enable more consistent height gain comparisons.

After the exclusion criteria were applied, 140 articles remained. Almost half of these were inaccessible, and many analyses were carried out on the same sources (notably the NordiNet outcomes study). Of those that could be used in

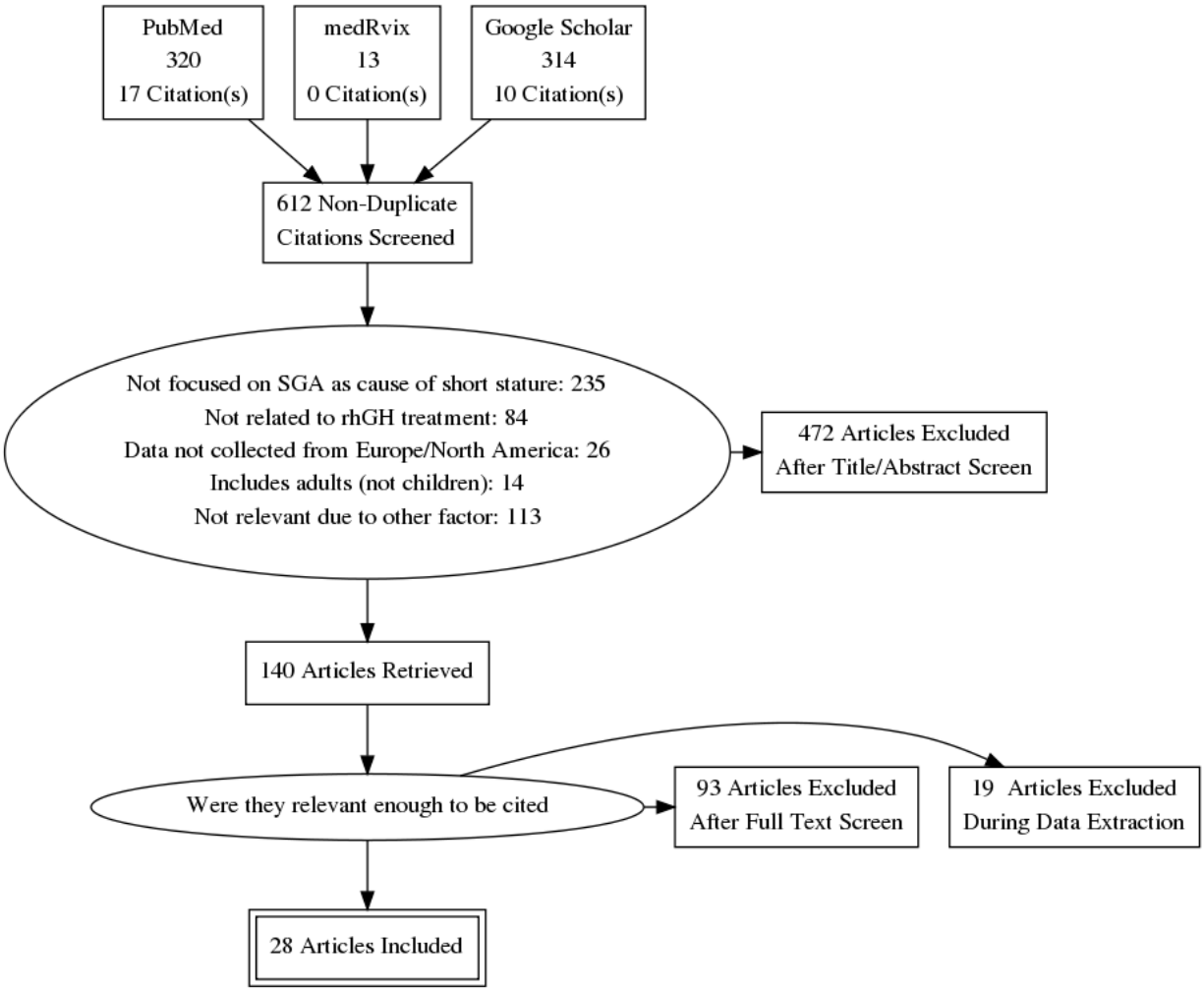

FIGURE 1: PRISMA flow diagram showing the process of the literature review.

the study, 28 were cited in the final literature review. The breakdown of this process is shown in figure 1.

Results

Results in terms of height/growth velocity increase and influencing factors

To evaluate the effectiveness of rhGH treatment, it is necessary to quantify the overall benefits of the treatment and weigh this against the costs and possible side effects. This is complicated by the fact that a 'good' height is subjective and the mean height of an average adult, accounting for sex, differs depending on the part of the world under review. In this review, I will consider the treatment successful based on how much it compensates for the catch-up growth that was not experienced by 10% of children born SGA before treatment began, and thus how far it closes the gap between the initial height (<2SD below the mean) and the mean weight and height of the local population accounting for age and sex. It should be noted that although height change being expressed in SDS is generally considered more robust across age and gender than expressing change in cm, change in height SDS is not completely age-independent, because less variation is observed in height SD in younger vs. older ages as demonstrated by Lee et al. (2012). To make the comparison more equal, this will only include European and North American subjects where the average height is comparable - with 5ft 10.1 inches (1.78 meters) average for males in

Europe and 5ft 9.69 inches (1.77 meters) in North America. (NCD Risk Factor Collaboration, n.d.)

The analysis of two ongoing studies by Lee et al. (2012) including the NordiNet® International Outcomes Study (NordiNet® IOS) and ANSWER encompassed 4,582 subjects aged <18 who underwent GH treatment for two years. Out of these, 678 subjects were born SGA (and as they qualified for GH treatment, it can be assumed they had not experienced catch-up growth). In the total population, the mean change in height SDS after one year of treatment, for all indications, was +0.57 SDS. However, children born SGA responded better to the treatment with height SDS of +0.64, only slightly lower than the +0.67 increase in SDS experienced by patients with MPHD (another cause of short stature). However, after two years of treatment, children born SGA and treated had experienced the greatest gain of +1.03 SDS which was higher than the increase in other groups and the mean of +0.99 increase in SDS. In total, 45% of those born SGA reached a normal height within ±2 SDS of normal height for age and gender. Although this percentage was higher for other groups in the study, the greatest height gain (and therefore likely the greatest benefit) was in children born SGA. The reason for the lower percentage reaching normal range despite the additional growth was due to children born SGA starting at a considerably lower baseline height in comparison to the other groups. It can therefore be inferred that GH therapy not only benefits children born SGA to a greater extent as they are more responsive to the treatment, but is also more needed for subjects in this category as they start with a lower baseline height. However, this lower baseline could be attributed to the labelling of SGA in Europe, as countries such as France required the child to be below -3SDS from the average height to qualify for medical reimbursement (Boguszewski et al., 2005).

Other studies provided further analysis of the full 10 years of the NordiNet® study. Although that study has not given final results, it shows the disparity in diagnosis in different countries affecting growth outcomes, with lower dosages in Serbia and Montenegro and higher dosages in France. It also confirms that dosages decreased over time in all countries and that children born SGA were shorter than all other groups treated with GH therapy at baseline with a mean height SDS values well below -2.5 (Polak et al. 2018). Another study identified the mean final height of a group of patients at -1.2 SDS as corresponding to 172cm in males and 159cm in females (Dahlgren & Wikland, 2005).

The response to GH treatment can differ according to a number of factors including initial height velocity, dosage, age when treatment started and duration of treatment, sex and adherence (Nicolino et al., 2018). In a French study, out of 51 SGA patients, 31 were good responders. These good responders were not only taller at the beginning of treatment and had better starting growth velocities, but they were also younger when treatment began. This suggests the treatment has greater effects when started at a younger age as children treated for >2 prepubertal years experienced a lower height gain when undergoing puberty (Dahlgren et al., 2005).

Adherence also plays a key role in the effectiveness of the treatment. This was shown in a study of 110 Spanish patients, which concluded that adherence to the treatment was generally very high at 93.9% over two years of treatment in SGA patients - but was also important in determining the end result, as the frequency of patients with a height velocity > 1 SD from the norm was higher (p=0.025) among patients with an adherence > 90% (de Arriba Munoz et al., 2020). It has been calculated that SGA children showed an increase of 0.6cm/year for each 10% adherence modification. Low adherence was observed in patients with lower pre-treatment height velocity and in patients whose parents had lower levels of education (Lee et al., 2019). In a survey of 116 subjects 75% of patients receiving rhGH treatment preferred the use of a new disposable pen, which is currently being introduced in the NHS in the UK, and if the new

FlexPro® pen delivery system fulfils its design to be easier to transport and use, it is possible adherence will increase among patients. When comparing two options of delivery devices, the NordiFlex (Norditropin) and GoQuick (Pfizer), it was concluded that the majority of patients preferred the NF to GQ and that the NF was more intuitive to use, as fewer mistakes were made using this mechanism (Kappelgaard et al., 2012). Finally, Sävendah et al. (2012) identified a significant difference between the genders in the 2-year response to GH treatment as well as in the prepubertal cohorts of SGA children. After correcting for dose, the mean baseline age and the initial height standard deviation scores, the change in height standard deviation scores was significantly greater in boys born SGA, suggesting a more varied response to treatment.

Results in terms of cost effectiveness

Over a patient's lifetime, somatropin (0.033 mg/kg/d) treatment was associated with a height gain of 16.12 cm and a cost per centimetre of height gained of £4,359. The incremental cost of somatropin treatment was £70,263, with a quality-adjusted life-years (QALY) gain of 2.95, resulting in an incremental cost per QALY of £23,807 - below the widely accepted cost-effectiveness threshold in the United Kingdom of £30,000 (Christensen et al., 2010). This study was focused only on children born SGA undergoing GH treatment, but it should be noted that it dates from 2010, so the cost per QALY may have decreased since.

When comparing adolescents born SGA without spontaneous catch-up growth, it was determined that the group treated with growth hormone scored significantly better in both health status and health-related quality of life in a disorder-specific questionnaire. This suggests that the boost in height provided by the treatment does translate into a better quality of life for the patient, which should be the true end goal (Bannink et al., 2005).

Other Effects of rhGH Treatment in Children Born SGA

The effects discussed will be outlined below:

1. Association of GH treatment with cardiovascular complications.

Two articles focused on the possibility of a link between childhood GH treatment and damage to the cardiovascular system. Tidblad et al. (2021) used a cohort study of 3408 patients treated with rhGH in childhood from 1985 to 2010 and followed up until November 31, 2014. It concluded that rhGH treatment was associated with increased risks of cardiovascular events in early adulthood (especially in women) but that conclusions of causality are limited, and overall risk remains low. Another study which assessed long term changes in blood pressure, lipid concentrations and carotid intima media thickness in order to assess cardiovascular risk factors in young adults born SGA after the cessation of GH treatment - but which only included 199 participants - came to the conclusion that long-term GH treatment in children born SGA has no unfavourable effects on cardiovascular health in early adulthood. The interpretation of the results even suggested that the treatment improved the lipid profiles of the patients (van der Steen et al., 2017).

2. Effect of the treatment on bone mineral density.

One study, which included 88 subjects and so had a relatively small sample size, used dual-energy x-ray absorptiometry to measure bone mineral density (BMD) and this was compared with BMI and target height. This study recorded an improvement in BMD over the course of GH treatment, with almost all children in the study having an end result adult BMD within the normal range (Annemieke et al., 2013). This is consistent with the results of another study by Willemsen et al. (2007) in which a six-year follow-up of a randomised controlled GH trial also using DXA to investigate body composition and concluded that

the treatment resulted in an increase in bone mineral apparent density (BMAD).

3. Metabolic implications including effects on insulin sensitivity and risk of diabetes.

In a study monitoring 26 children born SGA and treated with rhGH, it was concluded that there was no evidence to suggest future metabolic risk in young SGA children without catch-up growth, but that favourable changes in apolipoproteins were observed after one year of GH treatment in SGA children (Kojima-Ishii et al., 2018). A larger, randomised, double-blind trial with a population of 149 children born SGA from 8 different countries who received GH therapy delivered daily (using the NordiPen) found that GH only caused slight, non-significant improvements on total cholesterol and LDL cholesterol levels, although it maintains that longer GH treatment may be needed to explain the persistent benefits often reported in this regard. It also noted GH treatment reduced ghrelin levels through a negative feedback loop and so led to reduced fat mass, while glucose levels remained without the normal limits. It recorded a change in insulin levels, although this was reversible upon the discontinuation of the treatment, but further research is warranted to clarify the full effects (Lebl et al., 2011). It has been suggested that GH treatment results in higher fasting insulin and glucose stimulated insulin levels being observed and this is elevated with a higher dose of GH. Subjects born SGA also have an increased risk of developing diseases such as type 2 diabetes, hypertension, dyslipidemia and coronary heart disease and that the increased risk of type 2 diabetes may be a result of insulin resistance caused to SGA children having fewer β-cells. It is worth remembering that this lack of β-cells refers to all children born SGA (Delemarre et al., 2007).

4. Effects of GH treatment on Cognitive function and head circumference in children born SGA.

Studies on this topic are limited. Being born SGA has been associated with lowered intelligence and academic performance as well as behavioural problems. This randomised, double-blind trial of 79 children born SGA and treated with GH (with a mean duration of 8 years of treatment) showed a significant increase in Performal IQ and Total IQ and this increase was positively related to head circumference (Hokken-Koelega et al., 2006).

5. Effects on fat and fat redistribution.

After two years of GH treatment, children gained both weight and height and developed a less adipose body composition and these changes were accompanied by a more centripetal distribution of fat mass relative to those who did not receive treatment (De Schepper et al., 2007). Another study with a focus group of 35 short SGA children undergoing GH therapy (one group with a delayed start to treatment and another with a start not delayed for comparison) found that GH therapy contributed to not only a more normal body size and follistatinemia but also insulin resistance, hypo-HMW-adiponectinemia, hypertriacylglycerolemia and an amplification of the deficit in subcutaneous fat. The therapy moved height, weight and lean mass toward the norm. However, being born SGA is often associated with a high sensitivity to insulin and a low amount of subcutaneous fat, and the treatment led to an over-correction resulting in an insulin resilient state and an amplification in the deficit of subcutaneous fat (Ibáñez et al., 2010).

FIGURE 2: Table containing a summary of the effects of rhGH therapy in children born with SGA and a risk rating for each possible effect of the treatment.

Risk type	Effect	Additional notes	Risk Assessment
Cardiovascular risks	Increased risk of cardiovascular events	Often in women during early adulthood but no clear conclusions of causality	Low risk
	Changes in blood pressure	No unfavourable effects	No risk
	Changes in lipid concentrations	Treatment may improve lipid profiles	No risk
	Changes in carotid intima media thickness	No unfavourable effects	No risk
Effect on bone mineral density	Bone mineral density (BMD) / Bone mineral apparent density (BMAD)	Improvement in BMD / BMAD	No risk
Metabolic implications	Future/long term metabolic risk	No evidence to support future metabolic risk	No risk
	Changes in apolipoproteins	Favourable changes	No risk
	Changes to total cholesterol levels	Slight improvement	No risk
	Reduced fat mass	Reduces ghrelin levels through a negative feedback loop – leads to reduced fat mass	No risk
	Higher fasting insulin and glucose stimulated insulin levels while on treatment	Reversible on discontinuation - further research warranted	Medium risk – maybe linked to insulin sensitivity (see next point)
	Insulin resistance	May be an overcorrection of high sensitivity to insulin inherent in many children born SGA	High risk – could result in diabetes and heart problems
Effect on cognitive function	Increase in Performal IQ and Total IQ	May be linked to increased head circumference	No risk
Effect on fat / fat redistribution	Move toward the norm in weight and lean mass	Positive effect	No risk
	Amplification in the deficit of subcutaneous fat	Overcorrection to the lack of subcutaneous fat present in many children born SGA	Medium risk
	Development of a less adipose body composition	This is accompanied by a more centripetal distribution of fat mass relative to those born SGA and left untreated.	No risk
	Other abnormalities related to weight gain	Risk of developing hypo-HMW-adiponectinemia and hypertriacylglycerolemia	Medium risk

Discussion and Conclusion

This literature review aimed to evaluate the effectiveness of rhGH therapy in counteracting the effects of being born SGA and not experiencing catch-up growth. Although 634 results across 3 databases were screened and 140 of these results matched the inclusion criteria, after further screening by abstract and removing inaccessible or outdated articles, only 28 were cited. The particular lack of articles in MedRvix suggests that there have not been many recent additions to our understanding of the effects of GH treatment in children born SGA. This may change as the NordiNet® International Outcome Study and ANSWER programme® progress and more data is gathered on the overall effect of rhGH treatment, although the ANSWER programme is limited in the fact that the study is purely observational and may contain variations in data collection (Hoybye et al., 2013), (Rapaport et al., 2018).

Despite the lack of this long-term data, there is near unanimity that GH therapy provides an increase in growth velocity and moves the height of the subjects closer to the mean height for their age and sex. This change appeared to be particularly promising in those born SGA without catch up growth, and although fewer treated SGA children reached normal heights than those with other causes of short stature, this was due to them having a lower baseline height. The outcome of the treatment was affected by a wide range of factors, most notably the age that treatment started, gender and adherence. It also provided less benefit for those with the lowest starting height velocities and who likely would have benefitted most from more successful treatment.

Most of the effects not directly related to height are positive, as subjects have moved towards the norm in several areas including weight, lean mass, head circumference as well as Verbal IQ and Performal IQ. BMD also increased. Although there was a slight increase in the risk of cardiovascular complications in young adults treated with GH, this was minimal, and conclusions of causality are limited. The article claiming this (Tidblad et al., 2021) contradicted an earlier study by van der Steen et al. (2017) which claimed GH treatment has no metabolic downsides and in fact improves lipid profiles. Out of those discussed above, the most serious side effect is the over-correction of insulin sensitivity, resulting in insulin resistance and a higher likelihood of type 2 diabetes.

Overall, it appears the rhGH therapy is effective in improving the quality of life of children born SGA who did not experience catch-up growth and meets NHS guidelines on cost effectiveness. However, there is a lack of research on long term outcomes for the treatment, so this conclusion is limited to the first few years of treatment and further research is required.

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