Original Article

Efficacy and Safety of Biosimilar Growth Hormone in Indian Children

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Abstract

Objective: To study efficacy and safety of use of biosimilar growth hormone (GH) in Indian children with growth disorders. **Materials and Methods:** We studied 322 children (May 2012–2017) with growth disorders including growth hormone deficiency (GHD), multiple pituitary hormone deficiency (MPHD, idiopathic short stature (ISS), small for gestational age (SGA), and Turner syndrome (TS). Children were treated either with innovator molecule (Norditropin) or biosimilar GH (Headon) with standard dosage protocol for 1 year. Height and weight was measured using standard protocol. Height and BMI for age *Z*-scores (HAZ, BMIZ), height velocity (HV), and HV *Z*-score (HVZ) were computed from available data. **Results:** Mean age of the studied children (n = 322) was 9.6 ± 4.1 years, 32% children had GHD, 39% had ISS, 11% had MPHD, 12% had SGA, and 6% children had TS. There were no serious adverse events; three patients recorded eight instances of headaches, two had rash at injection site, and one each had hives and facial edema. Reactions were mild and were treated symptomatically. At the end of the 1 year of GH therapy, change in HAZ was similar in children from both the innovator and biosimilar GH groups. Similarly, the HV and HVZ were also similar in children from both groups and all the studied growth disorders. **Conclusion:** Biosimilar GH was effective and safe for treatment in children with growth disorders where GH use is indicated. However, in the view of scarcity of such data a longitudinal study with large sample size is warranted.

Keywords: Biosimilar GH, efficacy of GH, growth disorders, growth hormone, Indian children

Introduction

Growth hormone (GH) is essential for linear growth in children as well as for bone, muscle, and adipose tissue metabolism. In addition to growth hormone deficiency (GHD) and multiple pituitary hormone deficiency (MPHD), therapy with GH is also indicated in several non-growth hormone deficient disorders such as, idiopathic short stature (ISS), small for gestational age (SGA) children, skeletal dysplasia (SD), and Turner syndrome (TS). GH administration stimulates linear growth and increases growth rate in children with the above conditions.

Recombinant human GH (rhGH) has been available worldwide since 1985.[1] In recent years, biosimilar GH products have emerged as an option since the patent exclusivity for rhGH has expired.[2] The US Food and Drug Administration (USFDA) defines biosimilar as the biological product which is highly similar to the reference product notwithstanding minor differences in clinically inactive components; and that there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.[3] The biosimilar molecule is supposed to exert the same effect as the innovator molecule. The use of biosimilar GH has been approved in Europe in 2006.[2] In India, the use of biosimilar GH has been approved in 2008 and guidelines for their use have been laid down and then updated recently.[4]

Moreover, barring a few central government bodies such as the military who pays for GH for their employees only, GH is not covered in any state funding or health insurance system hence very few patients can afford GH in developing countries, such as India.[5] The use of biosimilar GH will be beneficial to patients on economic grounds. In India, the average cost of innovator GH per unit is approximately INR

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450 (approximately 7 USD and 6 Euros), while one unit of biosimilar GH costs approximately INR 250 (approximately 4 USD and 3 Euros), thus improving the affordability of treatment for patients. Thus, monthly expense for treatment for a child weighing 20 kg, would be approximately around Rs. 28,620 for innovator GH and Rs. 15,900 for Biosimilar GH.[6,7]

Although considered to be similar to the innovator structure, the biosimilar molecule needs to be tested in clinical settings for its safety and efficacy. However, data on the use of biosimilar GH for efficacy and safety of biosimilar GH in Indian children and in children with various GH indicated growth disorders is scarce. Hence, the objective of the present study was to assess the efficacy and safety of the biosimilar GH therapy in children with growth disorders and treated with GH, such as GHD, MPHD, ISS, SGA children, SD, and TS.

Materials and Methods

This was a 1 year prospective, observational study conducted at a tertiary care pediatric endocrine unit from Western Maharashtra, India. We studied a total of 322 children (9.6 ± 4.1 years) diagnosed with endocrine disorders indicating the use of GH therapy during May 2012 to May 2017. The study was offered to a total of 870 GH naïve children presenting at the pediatric endocrine unit (during May 2012 to May 2017) who were diagnosed with any of the following disorder 1. GHD, 2. ISS, 3. MPHD, 4. SGA, and 5. TS. Parents and children were asked to choose either innovator or biosimilar GH therapy [Figure 1]. Written informed consent was obtained from the parents and assent was obtained from children before commencement of the study. The study was approved by the Institutional Ethics Committee.

Inclusion criteria

Children with any of the following growth disorder: GHD, MPHD, ISS, SGA children, and TS who chose to take GH therapy with either innovator or biosimilar GH for a minimum period of 1 year.

Exclusion criteria

Children with a deficient GH secretion secondary to chronic illness (inflammatory bowel disease, cystic fibrosis, celiac disease, chronic asthma, chronic heart disease), hematological disorders like thalassemia, sickle-cell aaemia, malignancy, for example, craniopharyngioma and other intracranial tumors, chromosomal disorders like Down's syndrome, chronic steroid use or any other condition that is known to affect growth were excluded from the study.

Diagnosis of endocrine disorders

GHD: Children were diagnosed with GHD based on short stature (height-for-age *Z*-score (HAZ) <−2.0) and failure to mount a serum GH response >7 μg/L on two provocation tests using clonidine (0.15 mg/m^2) and glucagon (0.03 mg/kg) as stimulating agents prior to enrolment in the study. Estrogen priming was performed in peripubertal children.

ISS: ISS was defined auxologically as height <−2 SD for age, sex, and population without any evident cause of short stature after a thorough diagnostic evaluation. GH therapy was initiated in children with ISS with height <−2.25 SD with sufficient GH levels.[8]

SGA: SGA patients requiring GH therapy had birth weight, length, or both <−2 SD for gestational age, and demonstrated failure to catch up by 4 years of age and height <−2.5 SD for age and sex.[9] GH was started in SGA children in whom height was <−2.25 SD and 1 SD below the mid-parental height and who failed to catch up by 4 years.

MPHD: MPHD was diagnosed with patients having two or more anterior pituitary hormone deficiencies. GH stimulation tests were done once euthyroid state was established. Cortisol deficient patients were replaced with hydrocortisone first followed by GH treatment.

TS: TS was suspected by clinical presentation (short stature, delayed puberty, short or webbed neck, short 4th metacarpal or metatarsal, cubitus valgus), and diagnosis was confirmed by karyotyping.

GH therapy

All children from the innovator GH group were treated with rhGH (Norditropin; Novo Nordisk A/S Pharma, Bangalore, Maharashtra, India) and children from the biosimilar GH were treated with the rhGH (Headon; Somatropin), Sun Pharmaceutical Industries Ltd, Mumbai, India). The therapy included rhGH injection daily for a period of 12 months with an injection frequency of seven injections/week. GH dose was adjusted in accordance with the child's weight every 3 months. Children and parents were instructed to administer the rhGH at night. To record the compliance of therapy and/or any adverse events (AEs), parents and children were provided with a diary and asked to note down the administration as well as AE. Children were followed up with phone calls and text messages.

Standard dosage protocol as following was prescribed for GHD (dose 35 μg/kg/day, subcutaneously),[10] ISS (50 μg/kg/day),[8] SGA (45 μg/kg/day),[10] MPHD (30 μg/kg/day),[10] and TS (45 μg/kg/day).[10]

Anthropometric, pubertal staging, and bone age assessment

Standing height was measured using a stadiometer (Leicester Height Meter, Child Growth Foundation, London, UK, range 60 cm–207 cm). The reading was taken to the last completed mm, avoiding parallax and three such readings were averaged for analysis. Weight was measured using electronic weighing scales (Salter, Faridabad, Haryana, India) to the last 100 g. Height and weight were measured at baseline and at every 3 months till the end of 1 year of GH therapy. The anthropometric *Z*-scores were calculated using the ethnic reference values.[11] Height velocity *Z*-scores (HZZ) were derived with the use of available reference values.[12] Pubertal staging was performed by a trained pediatric endocrinologist using the Tanner method.[13,14] Bone age for all children

was assessed at baseline and at the end of 1 year of therapy from a radiograph of the non-dominant hand using the Tanner–Whitehouse method by a pediatric endocrinologist.[15]

Results

The study was offered to a total of 870 patients and a total of 322 patients chose to take GH (either the innovator or the biosimilar) and agreed to be a part of the study. Thus, we studied a total of 322 children (9.6 ± 4.1 years) with the following growth disorders in which GH therapy was indicated: GHD (n = 102; 32%), ISS (n = 126; 39%), MPHD (n = 36; 11%), SGA (n = 39; 12%), and TS (n = 19; 6%).

The mean compliance to GH therapy was 98% and was similar ($P > 0.1$) in all the disorders as well as between the innovator and the biosimilar therapy groups. Overall, seven patients (2%) reported AEs during the 1 year of therapy. Three patients (two on innovator and one on biosimilar) reported eight instances of headaches responding to painkillers. Two patients (on biosimilar) had maculopapular rash at the injection site, one patient (innovator) had facial edema subsiding within few hours, and one patient reported hives responding to anti-allergic medications. These AEs were mild and were treated symptomatically. On an average the AEs were mild and were similar in frequency in both biosimilar and innovator groups.

Baseline: The basic demographic and anthropometric characteristics of the children are described in Table 1 with respect to the GH therapy they were receiving. Majority of children from both the regimens (innovator GH: 60%, biosimilar GH: 73%) were prepubertal at baseline (similar in groups of all disorders) and remained the same at the end of 1 year of GH therapy. The GHD children who were on biosimilar GH therapy were older (mean age 10.5 years vs. 8.5 years) and had significantly lower mean height-for-age Z-score (HAZ) (mean HAZ − 4.5 vs. −3.2) ($P < 0.05$ for both). Similarly, children with ISS receiving biosimilar GH had significantly lower mean HAZ (−2.7 vs. −2.2, $P < 0.05$). However, no such differences were found in children with other growth disorders. Majority of children from both the groups were within reference range for their BMI-for-age Z-scores (BMIZ) [Table 1].

After 1 year of therapy (endline): At endline, there was a significant ($P < 0.05$) increase in height and HAZ score in all children from both the groups [Table 2].

To further study the response to 1 year of either innovator or biosimilar GH therapy the following parameters were computed: 'height velocity (HV)', 'height-velocity Z-score (HVZ)', and 'change in HAZ'. Also, the 'difference between the HAZ at 1 year and the mid-parental height Z-score' was calculated to assess whether there was any difference in the change in expected height between the two groups [Table 2].

The change in HAZ was similar ($P > 0.1$) between children receiving innovator or biosimilar GH from all disorders.

In GHD children, at the end of 1 year of study, the HAZ from innovator GH group was significantly greater than the biosimilar group (mean HAZ − 2.3 vs. −3.1, respectively, $P < 0.05$); but the change in HAZ was similar (mean change in HAZ 1.0 vs. 0.9, $P > 0.1$). Further, in these children, the mean HVZ was slightly lower in children on innovator GH than on biosimilar GH (mean HVZ 4.8 vs. 6.2, $P > 0.1$). These findings together may be attributed to the baseline low HAZ of the GHD children who chose the biosimilar GH therapy. In children from other disorders, the mean HVZ were similar between the two groups. Moreover, 'difference between the HAZ at 1 year and the mid-parental height Z-score was also found to be similar ($P > 0.1$) in children from all disorder groups on innovator versus biosimilar GH indicating that the change in expected height was similar between the two groups. There were no significant differences in the mean bone ages at baseline as well as at endline of the children from both the therapy groups (data not shown).

Discussion

Our results from the present study suggest that the response to biosimilar GH therapy for 1 year was similar to the innovator GH therapy in children with GHD, ISS, SGA, CPHD, and TS with a very few adverse events in both the treatment groups. Thus, indicating the efficacy and safety of biosimilar GH similar to the innovator GH.

As the patents for the innovator biopharmaceutical molecules have expired, the biosimilar products of the same molecule have emerged and many pharmaceutical companies have started their manufacturing. The initial approvals of the biosimilar were based on the quality, safety, and efficacy as compared to the reference molecule. Hence, post-marketing trials of

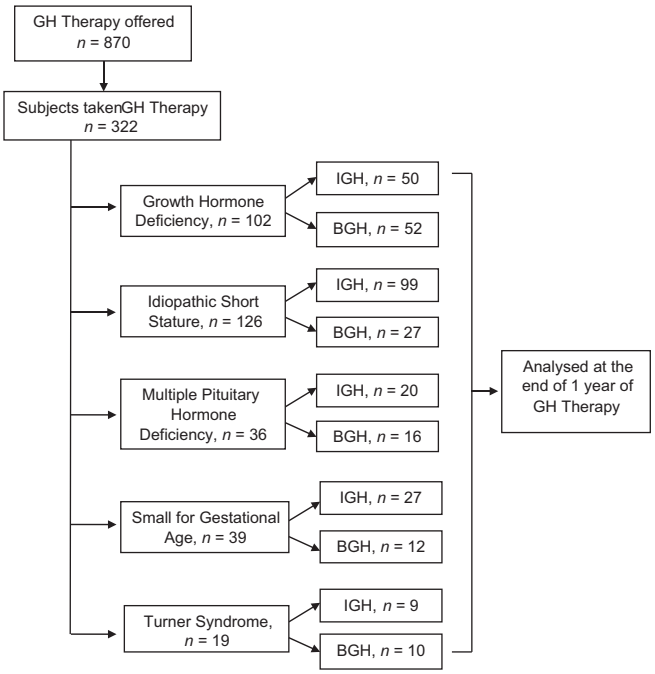

Figure 1: Consort diagram. IGH: Innovator Growth Hormone, BGH: Biosimilar Growth Hormone

Table 1: Baseline characteristics of the study children

	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m^2)	HAZ	WAZ	BAZ
GHD							
Innovator (*n*=50)	8.5±3.7	109.6±20.6	19.6±10	15.1±3	−3.2±1.3	−2.5±1.5	−0.8±1.1
Biosimilar (*n*=52)	10.5±4.2*	108.1±17.3	17.2±6.5	14.3±1.9	−4.5±1.7*	−3.7±1.4*	−1.3±1.1*
ISS							
Innovator (*n*=99)	10.4±3.4	124.7±21.3	26.9±12	16.3±3.4	−2.2±1.3	−1.6±1.4	−0.6±1.1
Biosimilar (*n*=27)	11.4±3.1	125.3±16.7	24.6±7.8	15.2±1.9	−2.7±1*	−2.3±1*	−1±0.8*
MPHD							
Innovator (*n*=20)	8.8±5.2	105.8±27.8	20.7±14.4	16.2±4.4	−4±2.2	−2.8±2.2	−1±1.9
Biosimilar (*n*=16)	10.2±6	109.9±26.9	22.5±12.3	17±3.2	−3.9±1.7	−2.5±1.7	−0.2±1.1
SGA							
Innovator (*n*=27)	6.2±3.4	96.8±21.3	13.6±7.4	13.4±2	−3.8±1.6	−3.7±1.9	−1.7±1.5
Biosimilar (*n*=12)	6.5±4.6	95.2±24.3	13.4±8.5	13.5±2.7	−4±1.4	−4±1.7	−2±1.6
Turner syndrome							
Innovator (*n*=9)	10.9±3.2	118.6±12.3	23.7±6.7	16.5±2.2	−3.2±1.2	−2±1.5	−0.3±1
Biosimilar (*n*=10)	11.2±2.4	119.3±10.6	25.8±6.7	17.8±2.9	−3.4±0.7	−1.8±1	0±0.9

*P<0.05

Table 2: Response to 1 year of GH therapy

	HAZ_1 year	Change in HAZ	HV_1 year	HVZ_1 year	Diff of HAZ at 1 year from MPH *Z*-score
GHD					
Innovator	−2.3±0.8	1±1.1	9.4±2.2	4.8±2.7	0.5±1.4
Biosimilar	−3.1±1.1*	0.9±0.8	10.4 ± 2.1!	6.2±2.8!	0.5±1.9
ISS					
Innovator	−1.7±1.2	0.6±0.8	8.3±2	4.8±3.3	0±1.5
Biosimilar	−2.2±0.6	0.7±0.5	8.7±1.9	6±3.7	−0.3±1.6
MPHD					
Innovator	−2.6±1.7	1.5±1.1	10±2.9	4.1±5	−0.1±1.8
Biosimilar	−2.6±1.3	0.9±0.7	10.2±2.9	5.3±2.8	0.2±1.8
SGA					
Innovator	−2.3±1.4	0.9±0.8	9.2±2	2.9±2.5	−0.2±1.6
Biosimilar	−2.7±1.2	0.7±0.4	8.8±1.2	4.2±3.9	0±1.4
Turner					
Innovator	−2.7±1.0	0.9±0.5	7.9±1.1	3.7±1.5	1.3±1.4
Biosimilar	−3.0±0.8	0.4±0.4	7.4±1.7	4±2.7	1.7±2.2

*P<0.05, !$P<0.1$

biosimilar GH are necessary.[16] In Indian markets, at least two biosimilar GH preparations are available namely Eutropin and Headon. In this study, the innovator GH used was 'Norditropin' which was a Somatropin (rDNA origin) injection, while, the biosimilar GH used was the injection 'Headon' which is synthesized from a strain of *Escherichia coli* (Recombinant DNA technology).

In concordance with our results in GHD children (mean HV: 10.4 ± 2.1, height velocity standard deviation score (HVSDS): 6.2 ± 2.8), a mean HV of 10.39 ± 2.5 and HVSDS of 5.52 ± 2.96 was also reported by 'Lyo study' after 1 year of biosimilar GH therapy in GHD children.[17] Further, in SGA children, at the end of 1 year of biosimilar GH therapy, Schwarz *et al*.[18] have reported a mean HVSDS of 4.16 which is similar to the mean HVSDS of 4.2 in our SGA children. Another study has shown no change in expected growth rates in children with GHD, ISS, and TS even after switching from innovator to biosimilar GH.[19] Very recent data from various long-term studies worldwide also suggest that the use of biosimilar GH in comparison to the innovator GH is efficient and safe in GHD children.[16] However, such data in other growth disorders are lacking.

One of the limitations of our study was that it was a pragmatic, clinic-based study and hence random allocation of patients to innovator and biosimilar GH could not be performed. Thus, the groups did not match in numbers (as the choice of GH treatment was made by the parents depending on their ability to afford the biosimilar or innovator); however, our study suggests that biosimilar GH is effective in promoting growth and also highlights the need for a randomized control trial for the same. Further, we present results from a 1-year study. For confirmation of our results and a better insight in the use of biosimilar GH, a longitudinal study is warranted.

Although we have reported data from the first year of GH therapy, to the best of our knowledge, this is the only study describing the efficacy and safety of biosimilar GH therapy in children with GHD, ISS, SGA, MPHD, and TS.

Conclusion

In conclusion, our study results indicate that biosimilar GH is safe and effective in Indian children in comparison with innovator GH. Lower cost of the biosimilar hormones may possibly make GH available to a large number of children in otherwise non-affording populations.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Pfäffle R. Hormone replacement therapy in children: The use of growth hormone and IGF-I. Best Pract Res Clin Endocrinol Metab 2015;29:339-52.
2. Saenger P. Ten years of biosimilar recombinant human growth hormone in Europe. Drug Des Devel Ther 2017;11:1505-7.
3. USFDA.: Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product Guidance for Industry. Available from: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM397017.pdf. Published 2016. [Last accessed on 2018 Jan 18].
4. Guidelines on similar biologics: Regulatory Requirements for Marketing Authorization in India. Available from: http://cdsco.nic.in/writereaddata/CDSCO-DBT2016.pdf (2016). [Last accessed on 2017 Dec 27].
5. Khadilkar VV, Khadilkar AV, Nandy M, Maskati GB. Multicentric study of efficacy and safety of growth hormone use in growth hormone deficient children in India. Indian J Pediatr 2007;74:51-4.
6. CIMS, 2018©. Available from: https://www.mims.com/india/drug/info/norditropin%20nordilet/norditropin%20nordilet%20pre-filled%20pen. [Last accessed on 2018 May 11].
7. ©2018 MedPlusMart.com. Available from: https://www.medplusmart.com/product/HEADON-4IU-INJECTION/HEAD0024. [Last accessed on 2018 May 09].
8. Cohen P, Rogol AD, Deal CL, Saenger P, Reiter EO, Ross JL, *et al*. Consensus statement on the diagnosis and treatment of children with idiopathic short stature: A summary of the Growth Hormone Research Society, the Lawson Wilkins Pediatric Endocrine Society, and the European Society for Paediatric Endocrinology Workshop. J Clin Endocrinol Metab 2008;93:4210-17.
9. Clayton PE, Cianfarani S, Czernichow P, Johannsson G, Rapaport R, Rogol A. Management of the child born small for gestational age through to adulthood: A consensus statement of the International Societies of Pediatric Endocrinology and the Growth Hormone Research Society. J Clin Endocrinol Metab 2007;92:804-10.
10. Wilson TA, Rose SR, Cohen P, Rogol AD, Backeljauw P, Brown R, *et al*. Update of guidelines for the use of growth hormone in children: the Lawson Wilkins Pediatric Endocrinology Society Drug and Therapeutics Committee. J Pediatr 2003;143:415-21.
11. Indian Academy of Pediatrics Growth Charts Committee, Khadilkar V, Yadav S, Agrawal KK, Tamboli S, Banerjee M, *et al*. Revised IAP growth charts for height, weight and body mass index for 5- to 18-year-old Indian children. Indian Pediatr 2015;52:47-55.
12. Tanner JM, Whitehouse RH, Takaishi M. Standards from birth to maturity for height, weight, height velocity, and weight velocity: British children, 1965. II. Arch Dis Child 1966;41:613-35.
13. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. Arch Dis Child 1970;45:13-23.
14. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. Arch Dis Child 1969;44:291-303.
15. Tanner JM, Healy MJ, Goldstein H, Cameron N. Assessment of skeletal maturity and prediction of adult height (TW3 method). In: Tanner JM, Healy MJ, Goldstein H, Cameron N, editors. W. B. Saunders; London: 2001. p.110.
16. López-Siguero JP, Pfäffle R, Chanson P, Szalecki M, Höbel N, Zabransky M. Ten years' clinical experience with biosimilar human growth hormone: A review of efficacy data. Drug Des Devel Ther 2017;11:1489-95.
17. Romer T, Peter F, Saenger P, Starzyk J, Koehler B, Korman E, *et al*. Efficacy and safety of a new ready-to-use recombinant human growth hormone solution. J Endocrinol Invest 2007;30:578-89.
18. Schwarz HP, Birkholz-Walerzak D, Szalecki M, Walczak M, Galesanu C, Metreveli D, *et al*. One-Year Data from a Long-Term Phase IV Study of Recombinant Human Growth Hormone in Short Children Born Small for Gestational Age. Biol Ther 2014;4:1-13.
19. Rashid N, Saenger P, Wu YL, Woehling H, Frankel M, Lifshitz F, *et al*. Switching to Omnitrope(®) from Other Recombinant Human Growth Hormone Therapies: A Retrospective Study in an Integrated Healthcare System. Biol Ther 2014;4:27-39.