ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 12, Issue, 10, pp. 59403-59406, October, 2022
https://doi.org/10.37118/ijdr.25472.10.2022

RESEARCH ARTICLE OPEN ACCESS

IMPACT OF ANASTROZOLE USE ON THE PREDICTION OF FINAL HEIGHT IN MALE ADOLESCENTS: A RETROSPECTIVE COHORT

***Renata Machado Pinto, Débora Ribeiro de Almeida and João Vitor Percussor Silva**

Universidade Federal de Goiás (UFG) - Departamento de Pediatria e Puericultura da Faculdade de Medicina da UFG

ARTICLE INFO

Article History:
Received 09th August, 2022
Received in revised form
21st September, 2022
Accepted 28th September, 2022
Published online 22nd October, 2022

Key Words:

Adolescents, Aromatase inhibitors,
Anastrozole, Short stature,
Near final height.

****Corresponding author: Renata Machado Pinto***

ABSTRACT

Introduction: The objective of this study was to evaluate the impact of the use of anastrozole (ANZ) in monotherapy or associated with growth hormone (GH) in the predicted of final height (PFH) and near-final height (NFH) of male adolescents with PEF below target familiar height (TH). ***Methods:*** This is a retrospective cohort. Data were obtained from medical records in a pediatric endocrinology service. ***Results:*** 75 patients between 11 and 14 years old participated in this cohort. Treatment with ANZ occurred for 1 year in 38.7%, 2 years in 40.0%, and 3 years in 21.3%. 76.0% used GH+ANZ, and 24.0% ANZ alone. TH and PFH at different treatment times showed a statistically significant difference, regardless of the use or not of GH. The ANZ group alone showed a mean increase of 5.73cm, 7.60cm, and 7.15cm in predicted height after 1, 2, and 3 years of ANZ. In the GH+ANZ group, this increase was 6.82cm, 10.27cm, and 7.44cm. Twenty-seven patients reached NFH, and in these, we observed a statistically significant increase concerning baseline PFH of 4.68 cm in the total group and 5.55 cm in the GH+ANZ group. **Conclusions:** The use of ANZ effectively increased PFH and NFH in adolescents with PFH below TH. However, the subgroup with concomitant use of GH had better outcomes.

Citation: Renata Machado Pinto, Débora Ribeiro de Almeida and João Vitor Percussor Silva, 2022. *"*Impact of anastrozole use on the prediction of final height in male adolescents: A Retrospective Cohort*", International Journal of Development Research,* 12, (10), 59403-59406.

INTRODUCTION

Children and adolescent's normal growth is a frequent concern among parents and caregivers, with short stature (SS) being one of the main reasons for looking for pediatricians and endocrinologists. The pathophysiology of SS may involve environmental, nutritional, hormonal and genetic factors that may act in isolation or in association between them. For didactic and therapeutic purposes, the SS study was divided into variants of normality (FSS - familial short stature and CDGP - constitutional delay in growth and puberty), idiopathic short stature (ISS), and various pathological causes, which include endocrinopathies, intrauterine growth retardation (IUGR), genetic and chromosomal syndromes, chronic diseases, malnutrition, pre-and post-natal disorders in addition to psychosocial origin.[1] The most crucial parameter in deciding whether to institute or not some treatment for SS is the prediction of final height (PFH). The Bayley-Pinneau (BP) and the TW-3 methods are known.[2] The expectation of low PEF commonly generates anguish for parents and frustration for adolescents, harming their quality of life. Thus, studies have emerged over the years that seek therapeutic options to increase the individual's final height.[3] The understanding that the final height of an individual depends on bone maturation created precedents for Gonadotropin-Releasing Hormone - GnRH (Gonadotropin-Releasing Hormone) analogs, a medication classically used in the treatment of precocious puberty, to be used in combination with Growth Hormone (GH). Therapy with GnRH analogs has shown efficacy in delaying epiphyseal fusion; however, its use is questionable since it makes young people hypogonadal in a critical moment of adolescence and the final height gain effect is controversial.[4] The question that followed was whether there was a way to interfere with epiphyseal fusion, with an effect of height gain and without such an essential impairment of hormonal function. Estrogen inhibition could be the answer to the question above. Since the 1990s, the critical role of estrogens in the maturation and closure of growth cartilage has been recognized[5], clinically evidenced by the observation of prolonged growth leading to an increase in final height in patients with a mutation in the gene that encodes the P450 aromatase enzyme, located on chromosome 15, responsible for the conversion of androgens to estrogens.[6] Aromatase inhibitors (AIs), drugs that interfere with the conversion of androgens to estrogens, have been used for more than three decades in patients with breast cancer since the marked suppression of plasma concentrations of estrogens improves the evolution of these tumors.[7] These drugs have become an option for the treatment of SS in boys with the advent of third-generation compounds: Anastrozole (ANZ) and Letrozole (LTZ),

which provide an aromatization block of almost 97% and 99%, respectively, prolonging the linear growth time by delaying the closure of bony epiphyses.[8] Clinical trials and retrospective cohorts over the last 20 years have indicated an effect on the delay of epiphyseal fusion and extension of longitudinal growth. In addition, such drugs help treat adolescents with ISS, advanced bone age, and reduced PFH, especially those who use AIs concomitantly with GH, indicating that their potential use leads to greater final height. In this way, AIs could be beneficial alone or in association with GH use; however, studies showing the effects on final height are still scarce.[9] The objective of this research is to evaluate the impact of the use of anastrozole (ANZ) in monotherapy or associated with growth hormone (GH) in the prediction of final height (PFH) and near-final height (NFH) of male adolescents with PFH below the familiar target height (TH).

METHODS

This longitudinal and retrospective study is based on secondary data obtained from patients' medical records from a pediatric endocrinology service in Goiânia - Goiás. Data were collected between July and September 2020 from medical records of patients consulted between January 2015 and September 2020.

Inclusion criteria were: male gender, Bone Age (BA) greater than or equal to 13 years, PFH below TH, and regular use of oral ANZ at a dose of 1 mg/day for at least 12 full months. The indication for the use of ANZ was the disproportionate acceleration of BA, leading to a reduction in PFH after puberty. Patients who used GH used it at a dose of 0.1IU/kg/day in the case of GH deficiency or 0.15IU/kg/day if the diagnosis was IUGR or ISS. The adolescents were clinically followed up by the same professional pediatric endocrinologist every 3 months when the GH dose was updated if necessary. The patient's height was measured using a fixed Tonelli E150-A stadiometer. Serum levels of blood glucose, total cholesterol, fractions, triglycerides, and testosterone were requested for all patients before and after starting ANZ. The method used to determine BA was the Greulich-Pyle method, and to calculate the PFH, we used the method based on Bayley Pinneau (BP). PFH was calculated based on the patient's height, divided by the growth fraction determined according to the BA obtained in this method.

For the calculation of PFH, the variation of up to 1 year of BA concerning chronological age was considered normal.Adolescents with a BA ≥ 16 years and a growth velocity ≤ 2 cm/year were considered to have reached NFH.

Statistical analyzes were performed using SPSS (Statistical Package for Social Science) version 26.0. Data parametricity was verified using the Shapiro-Wilk test. The demographic profile, weight, height, and treatment time were characterized according to GH through mean, standard deviation, absolute frequency, and relative frequency. The data distribution among children who had or did not have GH was verified by applying Student's t-test and Pearson/Posthoc chi-square test. The comparison of TH, PFH, BA, and biochemical parameters at different times were tested using the Friedman test followed by the Wilcoxon test with Bonferroni adjustment. A significance level of 5% ($p < 0.05$) was adopted in all analyses. The data used in this study were extracted from medical records, and their presentation was made numerically. Therefore, they did not allow the identification of patients or their families or the health service. The project of this work is registered in Brazil's Platform of the Federal University of Goiás (UFG), with the number CAAE 30175920.8.0000.5083.

RESULTS

After analyzing 81 medical records, 6 were excluded due to irregular medication use. Thus, the sample of this study consists of 75 male patients, aged between 11 and 18 years, who started treatment with ANZ with baseline BA between 13 years and 14 years and six months. Of these, 29 (38.7%) used it regularly for 1 year, 30 (40.0%) used it for 2 years, and the minor portion, 16 (21.3%) maintained regular use for 3 years of treatment. As for the concomitant use of GH, 57 (76.0%) used GH + ANZ, and 18 (24.0%) used ANZ as an isolated therapy. Data grouped in Table 1. The group of patients who underwent isolated treatment with ANZ was very heterogeneous, with diagnoses of ISS (8), FSS (7), Congenital Adrenal Hyperplasia (1), Precocious Puberty (1), and IUGR (1). On the other hand, most GH patients were diagnosed with GHD (47), and 9 had IUGR and 1 ISS. The dose was 0.1IU/kg/day for GHD and 0.15IU/kg/day for IUGR and ISS. Differences between TH, PFH at different treatment times, and NFH showed a statistically significant difference ($p < 0.001$), regardless of whether or not the use of concomitant GH. Data are shown in Table 2. Mean height predictions at baseline were: 170.05 cm, 167.19 cm, and 167.87 cm, relative to the ANZ-only, ANZ + GH-treated, and general study population group.

Table 1. Characterization of patients at the beginning of treatment

	Groups		Total N= 75	*P*
	ANZ N = 18	GH+ANZ N = 57		
Age (months)	151.50 ± 19.17	159.18 ± 13.35	157.33 ± 15.17	0.06*
Weight (kg)	42.94 ± 6.69	41.35 ± 6.20	41.73 ± 6.31	0.35*
Height (cm)	151.19 ± 5.61	147.37 ± 13.94	148.29± 12.53	0.26*
Time of treatment				
1 year	12 (66.7) †	17 (29.8)	29 (38.7)	0.02**
2 years	3 (16.7)	27 (47.4) †	30 (40.0)	
3 years	3 (16.7)	13 (22.8)	16 (21.3)	

*Test *t* of Student (Medium standard deviation); **Qui-square of *Pearson*; †*Posthoc;* n = absolute frequency; % = relative frequency

Table 2. Comparison in cm, between TH, PEF at different treatment times and NFH

Group	TH	PFH Basal	PFH 1 year	PFH 2 years	PFH 3 years	NFH	*p**
ANZ	172.33± 4.92	170.05± 5.48	175.78± 5.42	177.65± 4.35	177.20± 3.05	172.72± 3.42	<0.001
Δ PFH basal	- 2.28	Φ	5.73	7.6	7.15	2.67	
GH+ANZ	171.25± 4.68	167.19± 4.45	174.01± 5.15	177.46± 4.76	174.63± 7.34	173.45± 4.08	<0.001
Δ PFH basal	- 4.06	Φ	6.82	10.27	7.44	6.26	
Total	171.51 ± 4.73	167.87± 4.83	174.44± 5.23	177.48± 4.66	175.11± 6.74	173.32± 3.91	<0.001
Δ PFH basal	- 3.64	Φ	6.57	9.61	7.24	5.45	

*Friedman Test

Legend: Δ Baseline PFH – difference from baseline PFH; TH – target height; PFH – Predicted Final Height; NFH – near final Height

The respective groups had estimates below the TH by 2.28 cm, 4.06 cm, and 3.65 cm. Over the years of treatment, in those who used ANZ alone, there was a mean increase of 5.73 cm, 7.60 cm, and 7.15 cm in height predicted after 1, 2, and 3 years of ANZ, respectively.

Table 3. Comparison of TH, baseline PFH and height (in cm) in patients who reached NFH (N = 27)

	TH	Basal PFH	NFH	*p**
ANZ	173.10 ± 2.66	171.90 ± 2.50	172.72 ± 3.42	
(N = 5)				0.80
Δ Basal PFH	- 1.2	Φ	0.82	
ANZ+GH	171.87 ± 4.14	167.90 ± 3.21	173.45 ± 4.08	
(N =22)				0.01
Δ Basal PFH	- 3.97	Φ	5.55	
Total	172.10 ± 3.89	168.64 ± 3.44	173.32 ± 3.91	
(N = 27)				<0.00
Δ Basal PFH	- 3.46	Φ	4.68	1

*Friedman Test

Legend: Δ Baseline PFH: difference from baseline PFH; TH:Target Height; PFH: Predicted Final Height; NFH:Near Final Height

Table 4. Baseline biochemical parameters and 1 year after

	Basal	1 year	*p**
ANZ			
TC (mg/dL)	140.22 ± 20.98	134.89 ± 33.58	0.03
TG (mg/dL)	73.00 ± 28.17	60.89 ± 18.23	0.11
HDL(mg/dL)	44.89 ± 9.23	42.39 ± 7.64	0,21
LDL (mg/dL)	79.00 ± 14.50	80.33 ± 26.55	0.81
Testosterone(ng/dL)	252.89 ± 108.20	692.80 ± 255.00	<0.001
Glucose (mg/dL)	90.50 ± 6.25	88.61 ± 7.18	0.30
GH +ANZ			
TC (mg/dL)	150.26 ± 23.02	142.05 ± 20.91	0.003
TG (mg/dL)	76.93 ± 33.86	78.54 ± 24.86	0.55
HDL (mg/dL)	46.47 ± 7.39	43.02 ± 8.32	0.01
LDL (mg/dL)	89.56 ± 20.73	83.14 ± 19.12	0.003
Testosterone (ng/dL)	192.22 ± 88.36	675.91 ± 219.30	<0.001
Glucose (mg/dL)	90.07 ± 6.24	86.23 ± 6.97	0.001
Total			
CT (mg/dL)	147.85 ± 22.82	140.33 ± 24.48	<0.001
TG (mg/dL)	75.99 ± 32.44	74.31 ± 24.53	0.78
HDL(mg/dL)	46.09 ± 7.83	42.87 ± 8.12	0.004
LDL (mg/dL)	87.03 ± 19.85	82.47 ± 20.98	0.007
Testosterone (ng/dL)	206.78 ± 96.32	679.96 ± 226.68	<0.001
Glucose (mg/dL)	90.17 ± 6.20	86.80 ± 7.05	0.001

*Wilcoxon test

Legend: TC: total cholesterol; TG: triglycerides; LDL: low density lipoproteins; HDL: high density lipoproteins.

In parallel, this increase was 6.82 cm, 10.27 cm, and 7.44 cm in the group that associated ANZ with GH. The evaluation of NFH concerning baseline PEF showed a difference of 2.67 cm in the ANZ group alone and 6.26 cm in the group associated with GH, surpassing TH by 0.39 cm and 2.20 cm, respectively. The analysis that takes into account only the 27 adolescents who reached NFH, when compared to baseline PFH, the absolute increase in height was 0.82 cm in the ANZ group alone and 5.55 cm in the group associated with GH, reaching to surpass the TH by 1.22 cm in the whole group (Table 3). Among the laboratory data evaluated, there was an increase in average testosterone values between the introduction of AI and after one year of use. However, in addition to a relative reduction in the average cholesterol values, the other parameters remained close to the reference values for age and sex (Table 4).

DISCUSSION

This retrospective cohort study proved the increase in final height in male individuals with low PFH after using ANZ. This increase was both predicted and concrete. Comparison between estimates of final height data at different stages of treatment showed gains of: 5.73 cm, 7.60 cm, and 7.15 cm after 1, 2, and 3 years of ANZ alone. On the other hand, the group whose treatment associated ANZ with GH showed higher values (Table 2) in the same years of treatment. Similarly, Shams et al. conducted a retrospective study that observed that treatment time impacts the effectiveness of AI.[10] Review studies highlight the efficacy of AIs in delaying bone maturation with consequent increase of PFH and reinforce that the main limitation regarding the use of AIs in the treatment of SS lies in the inefficiency in demonstrating individuals' final height or NFH, which could question the practical validity of the formal indication of this medication.[11,12]

Pedrosa et al.identified NFH in 23% of their subjects, observing an average real gain of 2.6 cm.[9] Similarly, the present work demonstrated this data in about one-third of the total sample, and all, considering the general group, reached the genetic expectation of TH and exceeded the PFH demonstrated in the basal BP calculations (Table 3). Among adolescents who reached NFH, compared to baseline PFH, the absolute increase in height was 0.82 cm in the ANZ group alone and 5.55 cm in the group associated with GH, surpassing TH by 1.22 cm in the whole group. Analyzing the absolute data of NFH, a final height was observed on average 0.73 cm higher among those who used ANZ associated with GH, a statistically significant finding. This knowledge corroborates the literature, as demonstrated in the clinical trial by Mauraset al., 2016[4]and in the retrospective cohort by Miller et al., 2020.[13] In our study, it is also noteworthy that in all the years of follow-up, those who used GH concomitantly with AI showed greater adherence to treatment. Our hypothesis for such adherence was based on the fact that obtaining GH was only possible by periodically updating the reports performed by an endocrinologist, probably causing greater motivation to maintain regular specialized follow-ups. As for the drug's safety, a significant increase in testosterone levels was noticed since the first year of use. Since the first trials and reviews on the drug, such concern has been stated. On the other hand, the patients analyzed in the interim did not present significant lipid or glycemic profile abnormalities. The main limitation of the study was the heterogeneity of the patients, with a wide variety of clinical conditions and associated medications, a fact inherent to the retrospective nature of the research, similarly to what was highlighted by other authors.[9,12]Furthermore, the portion of the sample that used ANZ alone was markedly reduced among those who used it in combination with GH. Given the progressive increase in image cult and the rise of social networks, this work has an importance that goes beyond the verification of the effectiveness of the ANZ in increasing the prediction of final height. This study does

not focus its analysis on the subjectivity of the participants. However, it is known that providing adolescents with SS with an expectation of greater adult height impacts their quality of life and reduces frustrations and anxiety in the search for unsafe, ineffective, and possibly iatrogenic treatments.[3] Furthermore, the need to conduct a study focused on correcting the limitations present in this work and much of the available literature is reaffirmed. Therefore, we suggest conducting a prospective study of isolated use of AIs controlled with placebo, with a larger sample and follow-up until obtaining NFH. It will undoubtedly be able to discriminate better the groups that would benefit from such therapy. In addition, the impacts of increased testosterone should be detailed, as it is unclear whether these impediments to the approval of third-generation AIs in treating SS. Currently, third-generation AIs are used in the off-label use category, which restricts their use. However, once there is safety and scientific evidence, these must be standardized and regulated to expand their benefits to younger people.

CONCLUSION

In adolescents with low height prediction, the use of ANZ alone or associated with GH effectively increased the final height prediction. For example, in those who used ANZ alone, there was a mean increase of 5.73 cm, 7.60 cm, and 7.15 cm in predicted height after 1, 2, and 3 years, respectively. In parallel, in the ANZ + GH group, this increase was 6.82 cm, 10.27 cm, and 7.44 cm. In addition, taking into account only the adolescents who reached NFH, when compared to baseline PEF, the absolute increase in height was 0.82 cm in the ANZ group alone and 5.55 cm in the group associated with GH, surpassing TH in 1.22 cm in the entire group.

REFERENCES

1. Boguszewski MCS, de Martini AAC. Tratamento Hormonal da Baixa Estatura. Sociedade Brasileira de Endocrinologia. PROENDÓCRICO – Programa de Atualização em Endocrinologia e Metabologia: Ciclo 10. Sistema de Educação Continuada. Porto Alegre. *Artmed Panamericana*, 2018. V2, p. 131–164.
2. Costa KCM, Tomita I, Barbieri MA. Comparison of methods for final height assessment in adolescentswith a normal variant short stature. *J Hum Growth Dev*. 2017; 27(3): 288-293.
3. Bloemeke J, Balacano VR, Mauras N, Mericq V, Ross J, Permuy J, Quitmann J, Bullinger M. Psychometric performance of the Quality of Life in Short Stature Youth (QoLISSY) questionnaire in a randomized open-labelcomparatortrial in idiopathic short stature. *J Pediatr Endocrinol Metab.* 2019; 25;32(10):1089-1101. doi: 10.1515/jpem-2019-0137.
4. Mauras N, Ross JL, Gagliardi P, Miles Yu P, Hossain J et al. Randomized Trial of Aromatase Inhibitors, GrowthHormone, or Combination in Pubertal Boys with Idiopathic, Short Stature. *J Clin Endocrinol Metab.* 2016; 101(12):4984 – 4993 doi: 10.1210/ jc.2016-2891
5. Ferris JA, Geffner ME. Are aromatase inhibitors in boys withpredicted short stature and/orrapidlyadvancingbone age effective and safe? *J Pediatr Endocrinol Metab.* 2017; 1;30(3):311-317. doi: 10.1515/jpem-2016-0219. PMID: 28207416.
6. Fitas AL, Amaral D, Lopes L. Inibidores da aromatase em adolescentes do sexo masculino com baixa estatura idiopática. *Rev Port Endocrinol Diabetes Metab.* 2014; 9(1):53–58.. doi.org/ 10.1016/j.rpedm.2014.04.001
7. Wit JM, Oostdijk W. Best Practice & research. Clinical Endocrinology & Metabolism. 2015; 29(3):353-366. DOI: 10.1016/j.beem. 2015.01.003 PMID: 26051296
8. Leschek EW, Flor AC, Bryant JC, Jones JV, Barnes KM, Cutler GB Jr. Effect of Antiandrogen, Aromatase Inhibitor, and Gonadotropin-releasing Hormone Analogon Adult Height in Familial Male PrecociousPuberty. *J Pediatr.* 2017; 190:229-235. doi: 10.1016/j.jpeds. 2017.07.047. PMID: 29144249; PMCID: PMC5726420.
9. Pedrosa LF, de Oliveira JM, Thomé PRV, Kochi C, Damiani D, Longui CA. Height Increment and Laboratory Profile of Boys Treated With Aromatase InhibitorsWithor Without Growth Hormone. *Horm Metab Res.* 2017; 49(10):778-785. doi: 10.1055/s-0043-116944. Epub 2017 Aug 31. PMID: 28859208.
10. Shams K, Cameo T, Fennoy I, Hassoun AA, Lerner SE, Aranoff GS, Sopher AB, Yang C, McMahon DJ, Oberfield SE. Outcome analysis of aromatase inhibitor therapy to increase adultheight in males withpredicted short adultstature and/orrapid pubertal progress: a retrospective chart review. *J Pediatr Endocrinol Metab*. 2014; 27(7-8):725-30. doi: 10.1515/jpem-2013-0470. PMID: 24756052; PMCID: PMC4497551.
11. Cappa M, Cianfarani S, Ghizzoni L, Loche S, Maghnie M (eds): Advanced Therapies in Pediatric Endocrinology and Diabetology. Endocr Dev. Basel, Karger, 2016; 30:130-140. https://doi.org/ 10.1159/000439338
12. Hero M, Varimo T, RaivioT.Aromataseinhibitors in puberty. *Current Opinion in Endocrine and Metabolic Research.* 2020; 14:37-41. ISSN 2451-9650, https://doi.org/10.1016/ j.coemr. 2020.04.001
13. Miller BS, Ross J, Ostrow V. Height outcomes in children with growth hormone deficiency and idiopathic short staturetreated concomitantly with growth hormone and aromatase inhibitor therapy: data from the ANSWER program. *Int J Pediatr Endocrinol.* 2020; 2020:19. doi:10.1186/s13633-020-00089-z

****