Randomization to Letrozole vs. Anastrozole in Short Pubertal Males

NCT02137538

March 26, 2019

Laura Bachrach, Principal Investigator
E Kirk Neely, Principal Investigator
Stanford University
Stanford, California 94305

1. PURPOSE OF THE STUDY

a. Brief Summary

The purpose of the study is to determine if there are differences in the final height or hormone profile of patients placed on different forms of aromatase inhibitor now routinely used to increase stature; namely, Anastrozole and Letrozole. It also should determine if there are differences in the side effect profiles of the two drugs to be used.
Objectives

We hope to learn if there are differences in effects of different forms of aromatase inhibitors on growth. There have been 3 randomized controlled trials using aromatase inhibitors to improve stature in a variety of circumstances (delayed puberty, idiopathic short stature, growth hormone deficiency), but no actual comparative trials between the different forms. We hope to elucidate if there are differences in the growth rates/final heights between the different forms of therapy. This will certainly add to the current, somewhat small literature about the use of these drugs, although they are widely used. We also will look at the differences between the side effect profiles of the two medications. **Rationale for Research in Humans**

Since we are looking at final adult heights, human subjects are necessary.

2. STUDY PROCEDURES

a. Procedures

Patients from our endocrinology practice meeting our inclusion criteria will be consented into the study. They will be randomized into 1 of 2 treatment arms (Anastrozole 1 mg qday or Letrozole 2.5mg qday). Labs (gonadotropins, androgens, estrogens, growth factors, lipid profile) will be done every 6 months, bone age annually, and DEXA scans every 2 years.

We will see the patients annually until near final height (< 2 cm growth velocity per year), re-consenting in those over 18 years old. We will perform physical exams, obtain

anthropometric data, and repeat the above blood tests at least once off medication and perform imaging studies as warranted.

Beginning with this March 2016 renewal, we will no longer randomize to A vs L but use only A, continuing to collect observational data. **Procedure Risks**

We will be using the standard doses for the two drugs used. We will be monitoring with every 6 month physical exams and laboratory evaluation for possible side effects. At the discretion of the investigator, the medication may be reduced or discontinued, specifically if growth velocity falls below normal. **Use of Deception in the Study**

No deception will be used. **Use of Audio and Video Recordings**

No audio or video recording will occur. **Alternative Procedures or Courses of Treatment**

There are no alternatives to the above treatment. The only alternative would be to not start on the medication. Growth hormone is a theoretical option but is not standard of care for patients meeting these inclusion criteria. No standard treatment will be withheld. **Will it be possible to continue the more (most) appropriate therapy for the participant(s) after the conclusion of the study?**

Yes

g. Study Endpoint(s)

Our end point is final height which is defined as less than 2 cm of growth per year. We anticipate that all patients will reach this end point. **BACKGROUND**

a. Past Experimental and/or Clinical Findings

Without estrogen action, the fusion of the growth plates is postponed and longitudinal growth continues. This is the basic idea behind using aromatase inhibitors to augment growth. Aromatase inhibitors block the conversion of testosterone to estrogen leading to more time for skeletal growth. Although aromatase inhibitors have been used widely as a treatment for estrogen responsive breast cancers and in fact there is a plethora of data in that population, to date there have been 3 published randomized control trials using third generation aromatase inhibitors, and only one has been published to final height. The study to final height showed an increase of 6 cm in comparison to controls. The other studies are ongoing, but preliminary data is promising with improvements of standard deviation scores for height from baseline as well as improvements in predicted adult height based on bone ages. Finally, the available short-term data for safety are reassuring, however long-term data is lacking. **Findings from Past Animal Experiments**

NA

4. RADIOISOTOPES OR RADIATION MACHINES

a. Standard of Care (SOC) Procedures

Name of Exam	Identify if SOC or Research

Bone age	Standard of Care
DEXA	Standard of Care
Lateral spine film	Research

b. Radioisotopes

i. Radionuclide(s) and chemical form(s)

NA

ii. Total number of times the radioisotope and activity will be administered (mCi) and the route of administration for a typical study participant

NA

iii. If not FDA approved: dosimetry information and source documents (package insert, Medical Internal Radiation Dose [MIRD] calculation, and peer reviewed literature)

NA

c. Radiation Machines – Diagnostic Procedures

i. Examination description (well-established procedures)

Annual bone age x-ray, and lateral spine film at baseline and 2 years Setup and techniques to support dose modeling

Standard radiography

iii. FDA status of the machine and information on dose modeling (if procedure is not well-established)

Well established clinical radiography

d. Radiation Machines – Therapeutic Procedures

i. Area treated, dose per fraction/number of fractions, performed as part of normal clinical management or due to research participation (well-established procedures)

NA

ii. FDA status of the machine, basis for dosimetry, area treated, dose per fraction and number of fractions (if procedure is not well-established)

NA

5. DRUGS, BIOLOGICS, REAGENTS, OR CHEMICALS USED IN THE STUDY

a. Investigational Drugs, Biologics, Reagents, or Chemicals

Investigational Product 1	
Name:	NA
Dosage:	NA
Administration Route:	NA

b. Commercial Drugs, Biologics, Reagents, or Chemicals

Commercial Product 1	
Name:	Letrozole (no longer being used)
Dosage:	2.5 mg
Administration Route	Oral
New and different use? (Y/N)	Yes
Commercial Product 2	
Name:	Anastrozole
Dosage:	1 mg
Administration Route	Oral
New and different use? (Y/N)	Yes

6. PARTICIPANT POPULATION

a. Planned Enrollment

120; boys with short stature and/or growth hormone deficiency which may be congenital or acquired (post surgical or chemotherapy)

b. Age, Gender, and Ethnic Background

Males 10-17.99 years old, any ethnic background (identical to our clinical population) were recruited; those over 18 years old at f/u are reconsented,

c. Vulnerable Populations

The study is directed towards children because the purpose of the study is to evaluate growth. We will be monitoring for side effects closely.

d. Rationale for Exclusion of Certain Populations

All boys who fit under our inclusion criteria, regardless of ethnic background, will be included. Girls are excluded as aromatase inhibitor therapy will increase testosterone, causing untoward effects for girls.

e. Stanford Populations

None

f. Healthy Volunteers

None

g. Recruitment Details

The first person identifying patients for recruitment will be physicians in the Pediatric Endocrine Division at Lucile Packard. The protocol director will then continue the recruitment process in more detail.

h. Eligibility Criteria

i. Inclusion Criteria

Outpatient males with:
Age 10-17.99 years; re-consented if over 18 years old at follow up
Current height less than 5th percentile OR

Predicted adult height (based on bone age) more than 10 cm below target height (mid parental height)
Lab evidence of puberty: serum LH >0.3 IU/L and testosterone >15 ng/dl

ii. Exclusion Criteria

Bone age xray more than 14 years
FSH >20 IU/L

i. Screening Procedures

Pediatric endocrinologists will recruit all patients who qualify based on our inclusion criteria. Qualifying labs and bone age xray are usually obtained as part of routine clinical assessment of boys with short stature and/or delayed puberty, or would be obtained after enrollment and consent.

j. Participation in Multiple Protocols

We will ask the patients about other studies they may be enrolled in although we do not anticipate that this will occur.

k. Payments to Participants

No payments

l. Costs to Participants

Clinic visits, drugs, and laboratory charges which are considered standard of care will be the patient's responsibility.

m. Planned Duration of the Study

We anticipate the average length of treatment to be 2-3 years. We will evaluate the patients every 6 months with laboratory evaluation with the same frequency. After treatment, follow-up visits will be scheduled annually until growth is completed, which will be on average an additional 3-4 years (6-7 years from start of treatment). Subjects will be re-consented upon reaching 18 years of age.

7. RISKS

a. Potential Risks

i. Investigational devices

None

ii. Investigational drugs

None

iii. Commercially available drugs, biologics, reagents or chemicals

1) Arthralgia - reported in post-menopausal women at a frequency rate of 20-35%, lower in premenopausal women. Arthralgias have NOT been reported in the pediatric population.
2) Bone health - In adult women, there has been a reported decrease in bone mineral density by 6-7% after 5 years of therapy. We only have short-term data for young boys. Preliminary 1 year data did not show a difference in DEXA- measured bone mineral density in growth hormone (GH) deficient boys using Anastrozole in combination with GH. In boys with idiopathic short stature, there was no statistical difference between the treatment group using Letrozole versus the control group.
3) Fertility - In estrogen receptor knockout male mice, there is a progressive impairment of fertility. In one study using anastrozole in GH deficient boys, there was no difference in sperm parameters.
4) Metabolic parameters: lipids, insulin - In adult men with aromatase deficiency, increased cholesterol and increased insulin resistence has been descibed. In one study using Letrozole in pubertal boys, there was a significant decrease in HDL cholesterol, but all other lipids were unaffected. No changes have been reported in insulin sensitivity.
5) Higher than normal testosterone levels could cause hair loss or behavioral changes. Neither has been reported in studies to date.
6) Growth velocity - excessive reduction in growth rate, which seems more likely to occur during the suppression of estrogen levels with Letrozole therapy. Procedures

Blood draws at each visit. Bone age annually. DEXA scan and lateral spine film at baseline and two years into the study. Radioisotopes/radiation-producing machines

DEXA scan which has less radiation than a standard chest XRAY; bone age and lateral spine x-ray. Physical well-being

Routine clinical history. Psychological well-being

Routine clinical history. Economic well-being

None

ix. Social well-being

None

x. Overall evaluation of risk

Medium **International Research Risk Procedures**

NA

---

c. Procedures to Minimize Risk

We will be monitoring for arthralgia with the clinical history every 6 months. We will also collect laboratory data every six months: lipids, insulin levels, as well as estrogen and testosterone, gonadotropin and growth hormone levels. We will perform DEXA scans at baseline and two years into study to assess for decreases in bone density. Access to the labs/scans are all password protected.

---

d. Study Conclusion

The endpoint is final height. We will terminate when the growth rate has decreased to less than 2 cm per year. Since we will be monitoring clinical and performing physical exams every 6 months, if any of the side effects have been clinically significant, we will treat accordingly and/or terminate the use of the therapy.

e. Data Safety Monitoring Plan (DSMC)

i. Data and/or events subject to review

We will be monitoring, through laboratory evaluation, lipids, insulin sensitivity, gonadotropins, sex steroids, and growth hormone levels. We will monitor for changes in bone density through DEXA scans. Person(s) responsible for Data and Safety Monitoring

Protocol Director Frequency of DSMB meetings

All labs/scans will be monitored as soon as theyhave been received from the reference lab. Specific triggers or stopping rules

Physician's clinical assessment based on laboratory evaluation. DSMB Reporting

As needed

vi. Will the Protocol Director be the only monitoring entity? (Y/N)

Yes

vii. Will a board, committee, or safety monitor be responsible for study monitoring? (Y/N)

No

f. Risks to Special Populations

Short-term studies of aromatase inhibitors in this age group have not shown any significant risks, but there is a theoretical risk of issues with bone density, testicular function, and alterations to lipids/carbohydrate metabolism that is present. We will be monitoring for these risks during the course of the study. The direct benefit is increased ultimate height. We will be discussing these theoretical risks with the family in depth and will be obtaining assent from the subjects themselves. **BENEFITS**

Greater final height for the individual participant and possibly improved treatment options for future patients.

9. PRIVACY AND CONFIDENTIALITY

All participant information and specimens are handled in compliance with the Health Insurance Portability and Accountability Act (HIPAA) and privacy policies of Stanford University, Stanford Health Care, and Stanford Children’s Health.