IGF-1 and Bone Loss in Women with Anorexia Nervosa

NCT # 01406444

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PARTNERS HUMAN RESEARCH COMMITTEE
PROTOCOL SUMMARY

Answer all questions accurately and completely in order to provide the PHRC with the relevant information to assess the risk-benefit ratio for the study. Do not leave sections blank.

PRINCIPAL/OVERALL INVESTIGATOR
[redacted]

PROTOCOL TITLE
IGF-1 and Bone Loss in Women with Anorexia Nervosa

FUNDING
[redacted]

VERSION DATE
1.16.19

SPECIFIC AIMS

Concisely state the objectives of the study and the hypothesis being tested.

This protocol is a randomized, double-blind, placebo-controlled clinical trial which aims to investigate the effect of a sequential anabolic and anti-resorptive strategy on BMD in women with AN receiving estrogen. We hypothesize that a sequential anabolic and anti-resorptive strategy in AN will maximally increase BMD by first stimulating low bone formation with rhIG-1 administration and then decreasing bone resorption with risedronate.

Specific Aim 1: Sequential therapy with physiologic rhIGF-1 followed by a bisphosphonate will increase bone mineral density in women with AN more than a bisphosphonate alone or placebo.

Specific Aim 2: Sequential therapy with physiologic rhIGF-1 followed by a bisphosphonate will improve bone microarchitecture and bone strength in women with AN compared with bisphosphonate or placebo.

BACKGROUND AND SIGNIFICANCE

Provide a brief paragraph summarizing prior experience important for understanding the proposed study and procedures.

Anorexia nervosa (AN) is a prevalent serious disease of young women leading to severe bone loss at multiple skeletal sites. An increasingly common disorder among young women, AN is characterized by self-imposed restrictive nutritional practices and weight loss, occurring in 0.5-1.0% of college-age women in the US. The illness can persist despite psychiatric and nutritional counseling. Bone loss is a severe, frequent and often permanent comorbid medical complication of AN resulting in debilitating vertebral crush fractures. There are a number of compelling reasons why bone loss in women with AN is an important health concern. First, the prevalence, extreme rapidity and severity of bone loss results in major morbidity. Second, osteopenia is often permanent, despite recovery. Third, there are no therapies that normalize BMD or that are FDA-approved for bone loss in AN. Fourth, in contrast to postmenopausal osteoporosis in which

therapy may be life-long, the goal in patients with AN is treatment during the acute illness to reduce further bone loss and fracture risk. We propose that an early relatively short-term intervention during the period of low weight and rapid bone loss may prevent significant osteopenia and permanent increased fracture risk in women with AN.

Bone loss is prevalent and severe in young women with AN**.** The majority of women with AN have bone loss, and 50% have BMD measurements greater than 2 standard deviations (SD) below normative means. Bone mass in these young women may be comparable to postmenopausal women in their 7th and 8th decades. However, fracture risk is not fully explained by BMD, perhaps due to differences in bone microarchitecture between AN and healthy controls that is not captured by BMD. Of major importance is the fact that although BMD increases with weight recovery, osteopenia is often a permanent consequence of AN. Significant persistent osteopenia in women with AN has been shown in many studies and both cortical and trabecular BMD remain low more than ten years after recovery. Because bone mass remains persistently low despite recovery, such women remain at a high fracture risk throughout life, estimated to be 7.1 times that of healthy women in this age range. These data suggest that there may be a therapeutic window during which effective treatment should be implemented to prevent significant, lifelong bone mass reduction in this vulnerable population.

Low bone formation and high bone resorption underlie bone loss in AN. [redacted] AN in adult women is characterized by a negative balance in bone metabolism, with deceased bone formation and increased bone resorption. Unlike many other states of estrogen deficiency, bone formation is profoundly suppressed and bone resorption increased. This dissociation of bone formation and resorption is a key mechanism underlying the severe degree of osteopenia in this disease. Therefore, an ideal therapy for bone loss in AN must address both low bone formation as well as decreased bone resorption. [redacted] data demonstrate significant increases in BMD, but not to normal, with risedronate and with IGF-1, when administered separately, but neither alone addresses the severe degree of BMD observed in women with AN.

IGF-1 deficiency is a key etiologic factor underlying low bone formation and low bone mass in AN. Correcting IGF-1 deficiency effectively increases bone formation and BMD in AN. Based on [redacted], the scientific rationale for IGF-1 physiologic replacement in AN, and the demonstrated safety of IGF-1, rhIGF-1 is an ideal strategy for use as an anabolic agent in young women with AN. [redacted] data also provide strong evidence supporting the effectiveness of risedronate to decrease bone resorption and increase BMD in young women with AN. We hypothesize that bisphosphonates, because of their potent anti-resorptive effects, will consolidate the anabolic effects of rhIGF-1 to increase BMD in AN. We propose that maximal effectiveness to increase bone mass in AN will be achieved with sequential therapy with 6 months of rhIGF-1 followed by 6 months of risedronate. We propose that this therapy may be effective in reversing bone loss and increasing BMD during a time of active disease.

RESEARCH DESIGN AND METHODS

Briefly describe study design and anticipated enrollment, i.e., number of subjects to be enrolled by researchers study-wide and by Partners researchers. Provide a brief summary of the eligibility criteria (for example, age range, gender, medical condition). Include any local site restrictions, for example, "Enrollment at Partners will be limited to adults although the sponsor's protocol is open to both children and adults."

Subjects: Over the proposed 5 years, 200 women with AN will be recruited for an evaluable population of 90 women, 18-45 years old (assuming a 10% drop-out rate based on our previous studies). Subjects with AN will be randomized 2:2:1 in a double-blind fashion for 12 months: 1) sequential therapy with rhIGF-1 [redacted] for 6 months followed by 6 months of risedronate [redacted], 2) risedronate [redacted] or 3) double-placebo to determine effects on BMD, bone microarchitecture, and bone strength at trabecular and cortical sites. All subjects will meet the DSM-V criteria for AN and will be assessed for study suitability and monitored throughout the grant period for their overall psychiatric clinical state in coordination with the patients' clinical care team by a study psychiatrist, psychologist or psychiatric nurse practitioner. A standard oral contraceptive pill [redacted] or a standard transdermal estrogen patch [redacted] will be offered to potential subjects who are otherwise eligible to participate in the study but who are not currently receiving estrogen orally, transvaginally, or transdermally, nor have had their menses in the past two to three months. This medication will be prescribed at the lowest effective dose and for the shortest duration of time possible. Oral contraceptives or an estrogen patch will not be offered to any potential study participant with absolute or relative contraindications to estrogen use. We will not prescribe unopposed estrogen to any participant with an intact uterus. For such women who are not already receiving a progestin, we will concurrently provide [redacted]

Inclusion/Exclusion Criteria:

Inclusion Criteria, AN:

- Age 18-45 years
- AN defined by DSM-V diagnostic criteria
- Oral contraceptive use or transdermal or transvaginal administration of estrogen prior to the baseline visit, or willingness to start oral contraceptives or estrogen at baseline visit, or evidence that the patient is estrogen replete, i.e. menses within the previous two to three months
- BMD T score or Z score < -1.0 measured within 6 months of the screening visit.
- Normal TSH or free T4
- Normal serum 25-OH vitamin D (>=20 ng/mL) and calcium levels
- Ongoing care from a treatment team
- Agree to use barrier contraception
- Dental check up within the past year

Exclusion Criteria, AN:

- Any subject with contraindications to risedronate
- Any subject with binge-purge subtype of anorexia nervosa who vomits regularly as their form of purging (vs. those who use laxatives or diuretics) and who have significant periodontal disease, tooth erosion or an invasive dental or periodontal procedure within the previous three months.
- Any disease known to affect bone, including untreated thyroid dysfunction, Cushing's or renal failure
- Any medication known to affect bone metabolism within 3 months of the study, excluding oral contraceptives or other forms of estrogen administration. Bisphosphonates must have been discontinued for at least one year before participation
- Serum potassium <3.0 meq/L

- Serum ALT >3 times upper limit of normal
- eGFR of less than 30 ml/min
- Pregnant and/or breastfeeding
- Diabetes mellitus
- Active substance abuse, including alcohol
- Suicidality
- History of malignancy
- Angioedema to transdermal patch
- Hypersensitivity to estradiol
- Allergy to peanuts in subjects who will take progesterone tablets
- Breast cancer
- Known, suspected, or history, hypersensitivity to progesterone,
- Thromboembolic disorders
- Significant dental procedures are probable during the study year

An additional population of 50 women with AN who have BMD T score or Z score > -1.0 will be recruited for the bone microarchitecture substudy, for an evaluable population of 30 subjects. Exclusion criteria for the substudy will otherwise be the same as for the main study.

Briefly describe study procedures. Include any local site restrictions, for example, "Subjects enrolled at Partners will not participate in the pharmacokinetic portion of the study." Describe study endpoints.

Women with AN

Screening Visit: A "Screening Visit" will be conducted by a member of the medical team to determine eligibility for the protocol. All subjects will be seen [redacted] for an outpatient visit including the following: A complete medical history, physical examination and urine pregnancy test. History taking will include complete eating disorder, weight, menstrual, and medication histories. In addition, the following will be performed:

1. Blood draw for comprehensive metabolic panel, cbc, TSH or free T4, 25-OH vitamin D, phosphorus, and calcium level
2. Nutritional evaluation, including weight in a gown, height, frame size, calculation of percent IBW and body mass index (BMI), performed by research dieticians
3. An optional food diary will be given to subjects to fill out. This is optional for AN subjects, who could potentially experience psychological stress if required to complete food diaries.
4. DEXA scan of the spine, hip, radius, and total body if the subject has not had a DEXA scan within 6 months prior to the screening visit
5. Determination of AN diagnosis and subtype (restricting or binge/purge) using DSM-V criteria
6. Verification of the AN diagnosis
7. Verification of lack of comorbid concerns (i.e. suicidality, substance use) will occur by the study psychiatrist, psychologist, or psychiatric nurse practitioner. Suicidality is assessed through a verbal conversation with a psychiatric health professional. If the subject has been suicidal in the past, the psychiatric professional will ask questions to assess their level of

suicidality, and whether it would be a risk to their health to partake in a study. If a subject appears to be actively suicidal, study staff will reach out to their treatment team to alert them of this information and ensure that a treatment plan is in place. This plan includes if this information is discovered by screen via telephone.

Baseline Visit: Eligible study subjects (n=100 women with AN) will be assessed [redacted] for baseline testing.

1. A complete medical history including menstrual history and instructions on keeping a menstrual diary, consumptive habits (smoking, alcohol, caffeinated beverages) will be recorded, oral temperature, height and weight in gown, pulse and blood pressure, and physical examination will be performed
2. Urine pregnancy test
3. DEXA scan of the spine, hip, radius, and total body if screen visit did not take place within 1 month of BL visit or if a DEXA scan was not performed at the screening visit.
4. Baseline hormone and safety blood testing: IGF-1, glucose, ALT, potassium, PYY
5. HR-pQCT and FEA of the radius and tibia and single slice CT mid-thigh for muscle mass and cross-sectional abdominal CT at L4 for both visceral and subcutaneous abdominal fat mass respectively
6. MDCT of L1 to determine structural characteristics of the spine.
7. Functional tests of strength using the handgrip dynamometer
8. Subjects will be asked to take [redacted] calcium and [redacted] Vitamin D supplements daily throughout the study.
9. Eating Disorder Examination—Questionnaire
10. Eating Disorder Inventory-2
11. Paffenbarger Exercise Questionnaire

[redacted]

Eligible consented subjects will be allowed to have CT scans performed either 2 weeks before or 1 week after their baseline visit if scheduling conflicts arise with the baseline visit. This will allow the subject to obtain a baseline assessment of bone microarchitecture prior to the initiation of rhIGF-1 supplementation.

Randomization to treatment or placebo group will occur at the baseline visit. After the baseline visit, follow-up will occur at 1, 3, 4.5, 6, 7.5, 9, 10.5 and 12 months after baseline testing for follow-up testing. IGF-1 levels and glucose will be measured at each visit during the first 6 months of the study and rhIGF-1 dose titrated based on IGF-1 levels; IGF-1 will also be measured at 12 months. Pregnancy tests and clinical evaluation will be performed at each visit. A nutritional evaluation will be performed at every visit. BMD at the spine, hip, radius and total body will be performed at 6 and 12 months after baseline. HR-pQCT and FEA of the radius and tibia and cross-sectional CT to measure left thigh muscle mass and to determine abdominal fat mass (both visceral and subcutaneous) will be performed at 6 and 12 months. CT of L1 to determine structural characteristics of the spine will be performed at 12 months. Markers of bone

metabolism will be performed at months 1, 3, 6, 9 and 12. Functional tests of strength will be performed at months 6 and 12. The primary endpoint will be PA spine BMD.

Subjects who do not live locally will be able to have their blood drawn offsite for levels of IGF-1 and bone markers. Subjects who choose this option will also have a history and physical performed by a local physician for each offsite visit. For visits which involve questionnaires, those will be mailed to the subject to be completed and returned to study staff. Tests that need to be run in real time will be done at local laboratories, with the results mailed to investigators. Otherwise, the samples will be mailed to investigators. In the event that a CT cannot be performed on the scheduled visit date due to unforeseen issues, willing subjects will be able to return within a 1 month window for this test.

For studies involving treatment or diagnosis, provide information about standard of care at Partners (e.g., BWH, MGH) and indicate how the study procedures differ from standard care. Provide information on available alternative treatments, procedures, or methods of diagnosis.

No treatment thus far has been successful in increasing bone density in women with anorexia nervosa. Weight gain is associated with some increase in bone density, but is difficult to attain (occurs in only 50%) and sustain. The DXA scan is the best validated method currently used clinically to assess bone mass and fracture risk. This is the standard method of diagnosis at Partners, and is provided for free to study subjects. There are currently no FDA-approved therapies for anorexia nervosa-induced bone loss.

Alternate strategies to address low bone density in AN
Recovery of weight and menses: Although weight and menses recovery is associated with some increase in BMD, this increase is not sufficient to cause bone accrual to normalize, and BMD remains lower than in controls. Additionally, recovery can be hard to attain and sustain.

Calcium and vitamin D supplementation: Many studies have now shown that calcium and vitamin D supplementation is not sufficient to increase BMD in AN. BMD remains low in these women despite higher calcium and vitamin D intake than in controls

PTH: [redacted] increases BMD in post-menopausal women, however, PTH is not recommended in young people at this time given reports of osteosarcoma with PTH use in animal models.

Alternate strategies to assess bone microarchitecture and strength: MRI of the peripheral skeleton has lower resolution, longer scan time and increased susceptibility to image post-processing.

Describe how risks to subjects are minimized, for example, by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk or by using procedures already being performed on the subject for diagnostic or treatment purposes.

The intervention being provided involves no more than two shots a day given subcutaneously for a period of 6 months of a medication that has been shown to be safe in both adults with anorexia nervosa and in children with short stature and primary IGF-1 deficiency. Side effects, including

episodes of hypoglycemia, were uncommon in adult women with anorexia nervosa receiving rhIGF-1. Hypoglycemia is known to occur in anorexia nervosa per se, and was avoided in children receiving rhIGF-1 for short stature by administering the medication 30 minutes after meals. We plan to similarly administer rhIGF-1 30 minutes after breakfast and dinner. In a study [redacted] in 30 adult women with AN who received [redacted] rhIGF-1 [redacted], rhIGF-1 was well tolerated. Nadir blood glucose remained above 50 mg/dl after rhIGF-1 injection in all patients, and hypoglycemic symptoms were not reported acutely after rhIGF-1 injection or at any time throughout the study. Two subjects reported mild joint stiffness, which improved with dose reduction. In [redacted] study of adolescent girls with AN who received [redacted] rhIGF-1 [redacted], hypoglycemic symptoms were not reported. Other occasionally reported side effects of rhIGF-1 include bruising and redness at the injection site, lymphoid hypertrophy and snoring, lipohypertrophy, chronic middle ear effusions, raised intracranial pressure (headaches, vision changes, vomiting), slipped capital femoral epiphysis and progression of scoliosis in subjects who experience rapid growth, and arthralgias. Rotating injection sites will be advised and a close watch on other clinical features implemented. Also, as the drug is a pharmaceutical protein, anti-IGF-1 antibody formation can occur. 14 of 23 subjects treated for 2 years with the drug in one study experienced some degree of anti-IGF-1 antibody formation, though no clinical consequences (allergic reaction or loss of efficacy) were observed (from package insert). However, as with any exogenously administered protein, local or systemic allergic reactions may occur. Parents and subjects will be informed that such reactions are possible and that if an allergic reaction occurs, treatment should be interrrupted and prompt medical attention sought. Because we will be giving a smaller dose of rhIGF-1 [redacted], we expect to see fewer side effects than indicated in the package insert. These risks of side effects are justified in light of the anticipated benefit of improved bone density and lowered immediate and lifetime fracture risk with treatment during this acute phase of disease.

A number of procedures will be instituted to protect against potential risk involved in this protocol. All patients will have pregnancy tests on admission prior to receiving any radiation or study medication. Subjects will also have serial pregnancy tests at every study visit. All study-related serious adverse events will be reported to the Subcommittee on Human Studies within 24 hours of occurrence.

Describe explicitly the methods for ensuring the safety of subjects. Provide objective criteria for removing a subject from the study, for example, objective criteria for worsening disease/lack of improvement and/or unacceptable adverse events. The inclusion of objective drop criteria is especially important in studies designed with placebo control groups.

Subjects will be instructed to call us if they develop any side-effects of the IGF-1 or risedronate medication, or if symptoms of hypoglycemia are experienced. They will be advised to take 4 oz orange juice or two glucose pills if they are experiencing symptoms of hypoglycemia. Subsequent management will be decided based on the severity of the side-effect.

Serious side effects related to study drug will necessitate protocol discontinuation. If a subject develops a minor side effect, she will be asked to continue medications as per the protocol. Worsening of symptoms may necessitate temporarily withholding medication until other potential causes of symptoms are ruled out. Withholding medication for longer than one week will necessitate discontinuation of the study.

To minimize the risk from radiation, scans will not be performed on subjects until a negative pregnancy test result is obtained. If lab abnormalities are discovered, the subject and their physician, if authorized by the subject, will be notified.

If subjects are uncomfortable with any portion of any study visit, this portion will be discontinued or not performed.

Drop criteria for subjects:

1. Pregnancy (for any subject)
2. Medical instability, which will be determined by the study physician. Patients in this category will be assessed by the DSMB, and continue to be assessed according to study protocol
3. Serious study–related adverse event

FORESEEABLE RISKS AND DISCOMFORTS

Provide a brief description of any foreseeable risks and discomforts to subjects. Include those related to drugs/devices/procedures being studied and/or administered/performed solely for research purposes. In addition, include psychosocial risks, and risks related to privacy and confidentiality. When applicable, describe risks to a developing fetus or nursing infant.

Complications of surgical and non-surgical procedures: There is a risk of superficial bruising and discomfort at the venepuncture site. Rarely, fainting (from a vasovagal episode) or a treatable infection may occur.

Subjects will have DXAs to measure BMDs of the whole body, lumbar, spine, hip and radius during the study. This involves minimal radiation (~0.02 mSv for entire study), less than 1% of the background radiation received/person/year in the US. MDCT of the spine entails radiation of <1.8 0.9 mSv. The radiation dose of HR-pQCT of the radius and tibia is 0.06-0.08 mSv per measurement which is less than 2% of the annual background radiation from the earth and sky. The cross-sectional CT of the abdomen and mid thigh entails two CT slices and 0.18 mSv. The effective dose for three such scans in one year (baseline, 6 and 12 months) is about 18% of the dose an average person receives from background radiation in a year. The total effective dose from all radiologic exams for the entire study (4 DXAs, 3 HR-pQCTs, 2 MDCTs, and 3 thigh and abdomen cross-sectional CTs) will be slightly about 143% of the effective dose (3mSv) an average person is exposed to from background radiation per year.

There is no direct evidence that this amount of radiation exposure will cause harmful effects. To protect from scatter radiation during the MDCT, the patients will be asked to wear a lead vest and a lead skirt to minimize radiation to other parts of their body during scanning. Exposure of sensitive pelvic organs is not expected as only the L1 vertebral body is exposed. Pregnancy needs to be ruled out before these tests are done to avoid the risk of radiation exposure to the unborn baby. A urine pregnancy test will be performed prior to the x-ray for all subjects.

Complications of medications: rhIGF-1 will be administered [redacted]. RhIGF-1 is approved by the FDA for use in children with primary IGF-1 deficiency [redacted] As per the package insert for rhIGF-1 for this indication: mild or moderate hypoglycemia (very rarely

severe), thought to be related to the drug's insulin-like activities, may occur in up to 42% of patients on this medication during the course of therapy. More severe hypoglycemia is rare. Risk of hypoglycemia is generally avoided when a meal or snack is consumed 30 minutes prior to rhIGF-1 administration. All subjects will be familiarized with signs and symptoms of hypoglycemia and timely management of the same. Measures to treat hypoglycemia will be described (carry a source of carbohydrates at all times, e.g. a juice box or glucose tablets). Subjects with a serum IGF-1 level that is not within the normal range for age will receive a 25% dose adjustment. For those patients requiring a 25% dose increase to maintain IGF-1 levels within the normal range, we will contact subjects by phone to assess for side effects from the higher dose. We will monitor IGF-1 levels at all visits for all subjects taking rhIGF-1.

The potential risk of risedronate in this study is not greater than that associated with its common use in clinical practice. These risks include abdominal or stomach pain, skin rash, diarrhea, headache and joint pain. Less common side effects include severe abdominal pain or stomach pain, stomach cramping, belching, bone pain, blurred vision or change in vision, chest pain, constipation, cough, dizziness, dry eyes, fever, general feeling of discomfort or fullness, leg cramps, nausea, ringing in the ears, swelling of feet or lower legs, and weakness. On rare occasion, red sore eyes have been reported. Risedronate was well tolerated in the 16 women with AN who participated in [redacted] studies; there were no cases of esophagitis, despite a high prevalence of concomitant bulimia. Although the long-term risk of risedronate in young women is unknown, bisphosphonates have been used in premenopausal women to treat osteopenia due to glucocorticoids. In addition, these medications are used widely in the community and it is essential that their efficacy be assessed. Bisphosphonates remain in the bones for many years after administration, and it is unknown whether bisphosphonates may be secreted from bone during pregnancy or breastfeeding.

There may be other risks of rhIGF-1 and risedronate that are currently unknown.

Oral calcium can cause constipation and a metallic taste in the mouth.
Vitamin D in the doses being administered does not cause any side effects.
Estrogen can cause headache, breast tenderness, abnormal withdrawal bleeding, bloating and cramping, nausea and mood swings. The estrogen patch may also cause skin irritation. In a very small percentage of patients, blood clot or stroke have been reported.

EXPECTED BENEFITS

Describe both the expected benefits to individual subjects participating in the research and the importance of the knowledge that may reasonably be expected to result from the study. Provide a brief, realistic summary of potential benefits to subjects, for example, “It is hoped that the treatment will result in a partial reduction in tumor size in at least 25% of the enrolled subjects.” Indicate how the results of the study will benefit future patients with the disease/condition being studied and/or society, e.g., through increased knowledge of human physiology or behavior, improved safety, or technological advances.

[redacted]