Treatment of Osteogenesis Imperfecta with Parathyroid hormone and Zoledronic acid

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This study has been transitioned to CTIS with ID 2024-519705-36-00 check the CTIS register for the current data. The primary objective will be to investigate if a two-year course of TPTD followed by antiresorptive treatment with a single infusion of...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Metabolic and nutritional disorders congenital
Study type	Interventional

Summary

ID

NL-OMON55540

Source
ToetsingOnline

Brief title
TOPaZ

Condition

- Metabolic and nutritional disorders congenital
- Bone, calcium, magnesium and phosphorus metabolism disorders
- Bone disorders (excl congenital and fractures)

Synonym
brittle bone disease, OI

Research involving
Human

Sponsors and support

Primary sponsor: ACCORD

Source(s) of monetary or material Support: Eli Lilly,UK National Institute for Health Research

Intervention

Keyword: Osteogensis Imperfecta, Parathyroid hormone

Outcome measures

Primary outcome

Fractures validated by x-ray or some other form of imaging

Secondary outcome

Validated questionnaires:

Health Assessment Questionnaire

SF-36

Pittsburgh Sleep Quality Index

EQ-5D

Brief Pain Inventory

DNA and serum samples

Study description

Background summary

Osteogenesis imperfecta (OI) is an inherited skeletal disorder with a prevalence of about 11/100,000 which is characterised by an increased risk of fragility fractures (1). It is most commonly caused by mutations of the COLIA1 or COL1A2 genes which result in the production of collagen which is abnormal or present in reduced amounts although mutations in several other genes have been identified over recent years which can result in the same clinical phenotype (2).

The fracture risk in OI is at least an order of magnitude above that in patients with osteoporosis. Affected individuals are at increased risk of fragility fractures throughout life but the highest rates of fracture are

during childhood and above the age of 50 years (3). While affected individuals suffer tens or hundreds of fractures during their lifetime (2-4) there is relatively little information on fracture rate in prospective studies. A survey of adult patients with OI recently carried out in collaboration with the brittle bone society revealed that 79% of subjects had suffered a fracture during the previous 5 years, equivalent to an annualised fracture rate of about 16%. This is in keeping with data from randomised trials and observational studies, which on average, have reported an annualised fracture rate of about 17% (4-9).

Bone mineral density (BMD) is variable in patients with OI (10) and the increased risk of fracture is observed even in patients with normal BMD or osteopenia (3;4). However, a cohort study in Norway found that patients with BMD values in the osteoporotic range (T-score <-2.5) had a 3-fold higher rate of fractures than those with normal BMD or osteopenia (4). This is an important observation since it provides proof-of-concept that strategies aimed at increasing bone mass might reduce fracture rate in OI.

Bisphosphonates are frequently prescribed for patients with OI with the aim of preventing fractures but the evidence base for efficacy is poor. Previous Cochrane reviews and meta-analysis of trials in OI have concluded that while bisphosphonates consistently increased BMD in both children and adults the effects on fracture risk are uncertain (11-13). It remains unclear why the increase in BMD resulting from bisphosphonate treatment has not been associated with a consistent reduction in fractures. However one explanation might be that the increase in BMD that occurs with bisphosphonates is due mainly to increased mineralisation of bone, rather than an increase in the amount of bone tissue (14).

Recently a randomised placebo controlled trial with the bone anabolic agent teriparatide (TPTD) has been conducted in adults with OI with encouraging results (9). Not only did TPTD increase BMD when compared with placebo but the odds ratio of fracture was reduced in the active treatment arm, but not significantly (0.73; 95% CI 0.28-1.90). This study had a short duration of follow up however, and was not powered to detect a reduction in fracture risk. Another observational study of TPTD also showed encouraging results in OI patients previously treated with bisphosphonates but fracture data were not reported (5).

Study objective

This study has been transitioned to CTIS with ID 2024-519705-36-00 check the CTIS register for the current data.

The primary objective will be to investigate if a two-year course of TPTD followed by antiresorptive treatment with a single infusion of ZA in adults with OI reduces the proportion of patients who experience a fracture as

compared with standard care.

Study design

This will be a randomised controlled trial with an open design.
Following informed consent adult patients with a clinical diagnosis of OI will be randomised in a 1:1 ratio to receive treatment with TPTD for 2 years followed by an infusion of ZA with follow up for a further 2-3 years to to receive standard care for the duration of the study. Standard care may consist of no active treatment or bisphosphonates. The treatment strategy in the standard care group will be left to the discretion of the patients usual care provider.

The study will involve four scheduled visits over a 4-5 year period.

The duration of the follow-up will be determined by the rate at which fractures accumulate across the whole study population. It is expected that the duration of follow-up for individual patients will vary between 4-5 years.

Baseline: At the baseline/screening visit, patients will be provided with information about the study and invited to take part by providing written informed consent. A brief physical examination will be undertaken, along with medical history and documentation of current drug treatments. They will have safety bloods taken to ensure there are no contraindications to treatment and will have other bloods for genetic analysis and assessment of specialised biochemical markers of bone turnover. Participants will undergo a DEXA (dual energy x-ray absorptiometry) and spine x-rays and a special x-ray of the wrist called a high resolution quantitative computed tomography (HRpQCT) scan will be taken. Questionnaire will be completed by participants to assess bone pain, quality of life and functional status. Following completion of these tests, patients will be randomised into one of the treatment groups.

Participants in the TPTD group will be supplied with injection devices containing the treatment and trained in their use. The participant will self-inject the treatment on a daily basis for up to two years.

12 month visit
Safety and research bloods will be repeated, along with the participant questionnaire and a HRpQCT scan.

24 month visit
Safety and research bloods will be repeated, along with the participant questionnaire and a HRpQCT scan and a DEXA scan.

End of study visit
Safety and research bloods will be repeated, along with the participant questionnaire and a HRpQCT scan, DEXA scan and spine x-ray. Participants

reaching the end of their 24 month course of TPTD will have a ZA infusion scheduled.

Every 6 months for the duration of the trial all participants will receive a phone call from the research team to check for any adverse events and fractures.

Participants within the active treatment arm will also be asked to attend more frequently (approximately every 4 months) during the treatment period to pick up new supplies of TPTD and return used pens.

Intervention

24 months of teriparatide followed by a single infusion of zoledronic acid.

Study burden and risks

- 4 participant questionnaires
- 4 sets of blood samples (safety bloods and research bloods)
- 3 DEXA scans
- 2 spine x-rays
- 4 HRpQCT scans
- Daily injections of TPTD for 24 months if randomised to active treatment arm
- Single infusion of zoledronic acid if randomised to active treatment arm
- Daily completion of a pen injection diary 24 months if randomised to active treatment arm
- Completion of an event diary by all participants for duration of trial

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Adult patients age 18 years and above with a clinical diagnosis of OI, Patients willing and able to consent and comply with the study protocol

Exclusion criteria

•Current or previous treatment with an investigational (non-licensed experimental) drug with effects on bone metabolism within two years of screening or treatment with teriparatide within two years of screening., • Contraindication to TPTD or ZA , • Women of childbearing potential not using highly effective methods of contraception (see below), • Pregnancy, • Women that are breastfeeding, • Age <18 years, Women of childbearing potential (WOCBP) can be enrolled into the study but will be required to use highly effective methods of contraception (as defined by the HMA Clinical Trial Facilitation Group recommendations) before, during the trial if they are being treated with TPTD or bisphosphonates. Examples of highly effective contraception include:
• Established use of oral, injected or implanted hormonal methods of contraception.
• Placement of an intrauterine device (IUD) or intrauterine system (IUS).
• Bilateral tubal occlusion
• Vasectomised partner
True abstinence. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
Barrier methods of contraception (condom or occlusive cap (diaphragm or cervical/vault caps with or without spermicidal foam/gel/film/cream/suppository) are not considered to be highly effective

methods of contraception

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	20-01-2022
Enrollment:	50
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	alendronic acid
Generic name:	alendronic acid
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Disodium Pamidronate
Generic name:	Disodium Pamidronate
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Forsteo
Generic name:	Teriparatide
Registration:	Yes - NL outside intended use

Product type:	Medicine
Brand name:	Ibandronic acid 150mg
Generic name:	Ibandronic acid 150mg
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	zoledronic acid
Generic name:	zoledronic acid
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	19-11-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-01-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-07-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-08-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-10-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-10-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO Date:	23-03-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-04-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-10-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-11-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2024-519705-36-00
EudraCT	EUCTR2016-003228-22-NL
ISRCTN	ISRCTN15313991
CCMO	NL67979.029.19