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Understanding the mechanism of the acute phase response following intravenous (IV) bisphosphonates and its prevention: a study of the effects of zoledronic acid and co-prescription with fluvastatin or placebo

Submission date
04/04/2008

Recruitment status
No longer recruiting

Registration date
29/08/2008

Overall study status
Completed

Last Edited
05/04/2012

Condition category
Musculoskeletal Diseases

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[X] Results
[ ] Individual participant data

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
CZOL446H GB09

Study information

Scientific Title

Study objectives
That co-treatment of patients receiving potent nitrogen containing bisphosphonates (N-BP), with a statin, would prevent the activation and increase in gamma,delta-T cells and therefore prevent the subsequent acute phase response that occurs after the infusion of the N-BP.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Grampian Local Research Ethics Committee. Date of approval: 24/03/2005 (ref: 05/S0801/39)

Study design
Single-centre, randomised controlled trial.

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Osteopenia/ osteoporosis

Interventions
The participants will be randomly allocated to the following three arms:

Arm 1: Oral fluvastatin (40 mg immediate release formulation) immediately prior to an intravenous (iv) infusion of zoledronic acid (5 mg) + an oral dose placebo fluvastatin on the 1st and 2nd day after the infusion.

Arm 2: Single dose of matching placebo fluvastatin, immediately prior to an infusion of zoledronic acid (5 mg) and an oral dose placebo fluvastatin on the 1st and 2nd day after the infusion.

Arm 3: Oral dose of fluvastatin (40 mg immediate release formulation) immediately prior to an iv infusion of zoledronic acid (5 mg) + an oral dose of fluvastatin on the 1st and 2nd day after the bisphosphonate infusion.

Intervention Type
Drug

Phase
Not Specified

Drug/device/biological/vaccine name(s)

Bisphosphonates, zoledronic acid and fluvastatin.

Primary outcome(s)
Serum C reactive protein (CRP) at 72 hours.

Key secondary outcome(s))
1. Changes in cytokines (tumour necrosis factor-alpha [TNF-alpha], interleukin-6 [IL-6] and interferon gamma) at 24 hours
2. Changes in serum cholesterol at 48 hours
3. Alterations in temperature post infusion (at 24 hours)
4. Alterations in acute phase response as assessed by questionnaire at 72 hours

Completion date
30/04/2008

Eligibility

Key inclusion criteria
1. Postmenopausal women over the age of 20 and more than 12 months after cessation of menses or with serum estradiol and/or follicle stimulating hormone (FSH) levels consistent with a post-menopausal state, but <= 10 years post menopause
2. Bisphosphonate naïve women with osteopenia as defined by the World Health Organization (WHO) (T-score <= 1.0 but >-2.5) or osteoporosis as defined by the WHO (T-score <-2.5) at the lumbar spine or total hip Bone Mineral Density (BMD) measurement sites
3. Women willing and able to give informed consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
Female

Key exclusion criteria
1. The patient has a history of hypersensitivity to any statin or previously exposed to fluvastatin
2. The patient has a history of any illness or has significant abnormalities on pre-study clinical or laboratory evaluation which, in the opinion of the investigator, might either pose an unacceptable risk to the patient from participation in this study or complicate the interpretation of study data
3. The patient is a current user of any illicit drugs or has a history of drug or alcohol abuse within the past five years
4. The patient has a history of or evidence for metabolic bone disease (other than postmenopausal bone loss) including but not limited to vitamin D deficiency, hypoparathyroidism, primary hyperparathyroidism, recent hyperthyroidism (suppressed thyroid stimulating hormone [TSH] within the six months prior to entry into the study), Paget's disease

of bone, osteomalacia or renal osteodystrophy
5. The patient has any other disease potentially associated with increased bone turnover including, but not exclusive to, rheumatoid arthritis, Crohn's disease, severe renal impairment or severe hepatic disease
6. The patient has a history of cancer except for the following:
6.1. Superficial basal or squamous cell carcinoma of the skin which has been completely resected
6.2. Stage I breast cancer (lesion <= 3 cm with no nodal or local invasion) which has been completely treated more than one year ago with no evidence of recurrence
6.3. Other malignancies completely treated without recurrence or treatment in the last 5 years
7. Baseline renal insufficiency defined as either baseline creatinine of >177 mmol/l and/or calculated creatinine clearance of < 40ml/min
8. Serum 25-OH vitamin D level <15 ng/ml
9. Serum calcium <2 mmol/L and >2.75 mmol/L
10. Serum alkaline phosphatase >1.5x Upper Limit of Normal (ULN) and/or aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2 x ULN
11. The patient is receiving or has received treatment prior to randomisation which might influence bone turnover, including:
11.1. Any treatment with parathyroid hormone during the year prior to randomisation
11.2. Within the last 6 months: oestrogen, oestrogen analogues (e.g., raloxifene, tamoxifen), tibolone or anabolic steroids. Oestrogen taken >3 months ago for <= 1 week is acceptable. Topical (vaginal) oestrogen cream (<= 2 g) used up to two times weekly is acceptable
11.3. Thyroid hormone, unless on a stable dose for at least six weeks before randomisation with serum TSH within the normal range; patients found at screening to have mild hypothyroidism (as indicated by an elevation in TSH to no more than 15 µIU/ml) are eligible to enter the study provided they receive careful thyroid replacement therapy, if needed, and TSH levels are monitored three months later and as appropriate during the study
11.4. Glucocorticoid treatment for more than one month with >7.5 mg of oral prednisone (or the equivalent) per day within six months prior to randomisation; high-dose, intravenously within 6 months prior to randomisation; patients who have received therapeutic glucocorticoids in the past must be considered highly unlikely to require retreatment (with >7.5 mg of oral prednisone daily or the equivalent for more than one month or <= 500 mg of methylprednisolone pulse at any time) during the course of the study
12. Treatment with an immunosuppressant (e.g., cyclosporine, azathioprine) within the previous year
13. The patient is receiving or is expected to receive during the course of the study any medication (other than study medication) that might alter bone or calcium metabolism, including vitamin D in excess of 5000 IU per day, calcitonin, phenytoin, heparin, or lithium
14. HIV patients
15. No History of uveitis, iritis or conjunctivitis
16. No history of retinopathy or nephropathy especially in the presence of uncontrollable insulin dependent diabetes mellitus HB1AC >10%.
17. Any patient with severe dental problems or current dental infections, or with recent or pending surgery within 3 months of dosing

Date of first enrolment
01/06/2005

Date of final enrolment
30/04/2008

Locations

Countries of recruitment
United Kingdom

Scotland

Study participating centre
Division of Applied Medicine
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Sponsor information

Organisation
University of Aberdeen (UK)

ROR
https://ror.org/016476m91

Funder(s)

Funder type
Industry

Funder Name
Novartis Pharmaceuticals (Switzerland)

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/07/2011		Yes	No