Prophylactic zoledronic acid therapy to prevent or modify Paget's disease of bone progression in adults with SQSTM1 mutations: the ZiPP RCT

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Scientific summary

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Background

In Paget's disease of bone (PDB), the normal process of renewal and repair of the skeleton is abnormal, causing affected bones to enlarge and weaken, resulting in pain, deformity, fractures, secondary osteoarthritis and deafness. People with PDB often present when the disease at an advanced stage with irreversible bone damage. The main treatment option is bisphosphonates, which significantly reduces the increased bone turnover associated with PDB, as well as reducing the associated pain in some patients. However, bisphosphonates cannot reverse bone deformity, deafness or arthritis in PDB with the result that symptomatic benefits are often blunted in people with advanced disease.

The most important susceptibility gene for PDB is *SQSTM1*. Mutations of this gene are observed in up to 40% of individuals with a family history of PDB and up to 15% of those who are unaware of a family history (Makaram NS, Ralston SH. Genetic determinants of Paget's disease of bone. *Curr Osteoporos Rep* 2021;**19**:327–37). Carriers of *SQSTM1* mutations have been shown to have more severe disease with an earlier age of onset than those who do not have such mutations. It has been estimated that about 80% of *SQSTM1* carriers may develop PDB by the time they have reached their seventh decade [Morissette J, Laurin N, Brown JP. Sequestosome 1: mutation frequencies, haplotypes, and phenotypes in familial Paget's disease of bone. *J Bone Miner Res* 2006;**21**(Suppl 2):38–44].

The zoledronic acid (ZA) to prevent the development of Paget's disease [(zoledronic acid in the prevention of Paget's disease (ZiPP)] trial was a double-blind, placebo-controlled randomised study aimed to determine if therapeutic intervention with a single infusion of 5 mg ZA would favourably alter the progression of PDB in people with a family history of PDB who test positive for *SQSTM1* mutations, but who had not yet been diagnosed with PDB.

Objectives

The primary objective was to determine if ZA could prevent the development of bone lesions with the characteristics of PDB in people who carry *SQSTM1* mutations. Additional objectives were to determine if ZA could modify the appearance of existing PDB lesions; modify biochemical markers of bone turnover; modify quality of life, bone pain, anxiety and depression; or modify the risk of complications related to the development of PDB.

Methods

The ZiPP trial was a randomised, double-blind placebo-controlled trial conducted in 25 centres from 7 countries worldwide. A genetic screening programme was offered to 1307 people with a family history of PDB and 750 agreed to be tested. This resulted in the identification of 350 individuals who were carriers of *SQSTM1* mutations but who were not known to have developed PDB. Of these, 222 (63.4%) consented to participate in the study. At the baseline visit, a radionuclide bone scan was performed to detect the presence of bone lesions with the characteristics of PDB; blood samples were taken for analysis of biochemical markers of bone turnover and questionnaires were completed to assess pain, health-related quality of life and anxiety or depression. Participants were then randomly allocated to receive a single infusion of the bisphosphonate ZA 5 mg intravenously or an identical placebo. Both groups were followed up annually where blood samples and questionnaires were repeated. Adverse events (AEs) were recorded on a continuous basis. At the end of study, the bone scan was repeated, bloods were taken for assessment of biochemical markers and questionnaires were repeated.

Results

At baseline, 21/222 individuals (9.5%) already had evidence of PDB on bone scans. Two out of 90 individuals (2.2%) allocated to placebo developed new bone lesions compared with 0 out of 90 (0%) allocated to ZA {odds ratio [OR] = [OR 0.41, 95% confidence interval (CI) 0.00 to 3.43; $p = 0.25$]}. Eight participants in the placebo group had a poor outcome (lesions that were new, unchanged or progressing) compared with none in the ZA group (OR 0.08, 95% CI 0.00 to 0.42; $p = 0.003$). In the ZA group, 13/15 lesions present at the start had disappeared compared with 1/29 lesions that disappeared in the placebo group ($p < 0.0001$, between groups). One participant allocated to placebo required treatment with ZA due to the emergence of symptoms related to PDB. Biochemical markers of bone remodelling were significantly suppressed by ZA. For plasma type I collagen C-terminal telopeptide (CTX), which is a marker of bone resorption, the estimated least squares mean [95% CI] treatment difference taking all timepoints into account was −0.09 [−0.12 to −0.07] ($p < 0.0001$) in favour of ZA. For plasma procollagen type I amino-terminal propeptide, which is a marker of bone formation, the estimated treatment difference was −16.32 [−22.05 to −10.59] ($p < 0.0001$) also in favour of the ZA group. Finally, for serum bone-specific alkaline phosphatase (BAP), another marker of bone formation, the estimated treatment effect was −1.68 [−2.59 to −0.78]; $p = 0.0003$ in favour of ZA. There was no significant difference between the groups in quality of life, bodily pain, or anxiety and depression, and no difference between the groups in AEs or serious adverse events (SAEs).

Limitations

The study had some limitations. First, 9.5% of participants already had Paget's disease, reducing the power to detect treatment effects. Second, only two participants developed new lesions compared to the 15% expected. The small number of events meant that the study was not powered to meet the primary outcome. In addition, the small number of events meant that the study was unable to analyse the data by logistic regression to adjust for covariates or family clustering as was initially planned. This estimate was based on limited cross-sectional data on the increasing PDB incidence with age.

Conclusion

The trial has shown that genetic testing for *SQSTM1* mutations coupled with bone scan examination can detect early PDB in those with a family history of the disorder. It also shows that ZA treatment can favourably modify the evolution of PDB in this participant group. The offer of genetic testing for *SQSTM1* coupled with bone scan examination and targeted intervention with ZA can modify the evolution of PDB in those with a family history of the disorder. Further research is required to evaluate the clinical and health-economic benefits of this approach in the longer term. Further research with an extended follow-up in the ZiPP- long term extension (LTE) study is in progress, and it will provide valuable information on the duration of the effects of a single infusion of ZA on those with existing lesions and the development of new lesions in both treatment groups. Although this was an experimental medicine study, it will now be important to consider a health-economic analysis to try to model the effects of genetic testing, bone scanning and ZA treatment in this participant group to evaluate the likelihood of long-term clinical and symptomatic benefits.

Study registration

Current Controlled Trials ISRCTN11616770.

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