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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Plain language summary

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Paget's disease of bone causes bones to enlarge and become more fragile, potentially leading to pain, deformity, fractures, osteoarthritis and deafness. In normal clinical practice, Paget's disease of bone is often diagnosed at a late stage during the course of the disease when bone damage is irreversible. Early diagnosis and treatment may be beneficial. Mutations in the *SQSTM1* gene can cause Paget's disease of bone to run in families and people with Paget's disease of bone who carry these mutations have more severe and extensive disease with an earlier age at onset. In this study, genetic testing for *SQSTM1* mutations was offered to 1307 people with a family history of Paget's disease of bone with 750 individuals agreeing to be tested. Of these individuals, 350 (46.7%) were found to carry *SQSTM1* mutations and were invited to take part in the trial; 222 people accepted and were enrolled into the study. They were randomly assigned to receive the drug zoledronic acid or a placebo. Both groups were followed for about 7 years. At the start of the study, 9.5% of participants already had Paget's disease of bone lesions. Over time, two people on placebo developed new lesions compared to none on zoledronic acid. In the placebo group, eight people had poor outcomes such as new or worsening lesions versus none in the zoledronic acid group. Treatment with zoledronic acid made existing lesions disappear more often than placebo. One person on placebo required treatment with zoledronic acid as they developed Paget's disease of bone-related symptoms. The study showed that it is feasible to identify people with early Paget's disease of bone by genetic testing coupled with bone scan examination in those with a family history of Paget's disease of bone. Treatment with zoledronic acid caused existing lesions to disappear more often than placebo. Genetic testing for *SQSTM1* mutations coupled with bone scan examination and prophylactic zoledronic acid treatment may be beneficial in people with a family history of Paget's disease of bone.

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