Scottish Government Health Directorates Chief Scientist Office

CHIEF SCIENTIST OFFICE

FOCUS ON RESEARCH

TITLE

Researchers
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Aim
Teriparatide (TPTD) is a highly effective treatment for osteoporosis, but it is not widely used because treatment costs are high and the response to treatment is variable. We have gained evidence to suggest that genetic profiling could identify good and poor responders to TPTD, but this needs to be validated. The aim of this grant proposal was to determine whether genetic profiling could really be of clinical value in identifying patients who respond well (or poorly) to TPTD, so therapy can be better targeted.

Project Outline/Methodology
We collected 468 patients with severe osteoporosis from centres in UK, Denmark and Slovenia, treated with TPTD between 18-24 months.
We investigated more than 6 million of genetic markers distributed along the whole genome on these patients, by genome-wide association analysis, and checked whether they were statistically associated with response to TPTD, measured as increase on bone mineral density (BMD) at lumbar spine and femoral neck.

Key Results
Analysis of genetic markers detected a significant association between a signal on chromosome 2 and the response to treatment. It was found that patients who did not carry the marker had 2-fold increase in bone mineral density (BMD) at lumbar spine than the patients with two genetic copies of the marker. In addition, we identified two markers at chromosomes 15 and 19, which showed a trend of association with the response to TPTD. Combined genetic information from these three markers showed a strong association between the number of markers and the poor response to treatment (patients with 3 or more markers had an increase of 3% in LSBMD, while patients without any marker had more than 18% increase in BMD).
The strongest signal, on chromosome 2, appoints to *CXCR4* gene, as associated with response to TPTD. This gene is known to play a role in bone metabolism, by regulating WNT signalling, the most important pathway involved in bone formation.
The response of TPTD at femoral neck was subtle, and our study showed limited power to detect true signals, identifying only a trend of association with several markers in different chromosomes.

Conclusions
We have successfully developed a genetic tool to predict good response to teriparatide. In this way, the treatment for osteoporosis could be personalised, and target a high cost drug more efficiently.
Besides, this study has identified *CXCR4* gene as playing a role in the response to TPTD, which makes it a potential candidate to develop new therapeutic targets.

What does this study add to the field?
To date, there are no means to predict the response to teriparatide treatment before the patient has initiated the treatment. Here, we propose a simple DNA test to identify good or poor responders, which could help the clinicians to personalise the treatment depending on the genetic background of the patient.

Implications for Practice or Policy
TPTD is very expensive and requires a big commitment from patients. However, there is a high variability in response to the drug; in many cases not better than the standard care, which is cheaper and easier to administer. The method we propose could be easily implemented in routine practice as a tool for the clinicians to decide to include the patient in the TPTD treatment, targeting this costly drug to those patients who benefit the most.

Where to next?
We need to validate the method proposed using a different group of patients, to confirm its efficiency as predictive tool.
We also want to gain knowledge on the role of CXCR4 in bone formation and how this gene is involved in the response to TPTD, which could help to identify new theraputic targets for osteoporosis treatment.

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