

Are We Treating Paget's Disease Effectively?

By Dr Charles Hutton, FRCP, MBChB

Consultant Rheumatologist, Derriford Hospital, Plymouth

One of the many frustrating problems for patients with Paget's disease is knowing whether or not drug treatment will moderate long term complications. This frustration may also be shared by their clinicians and may lead to a pessimistic attitude to intervention with the result that some patients may not have the opportunity of at least being considered for active treatment.

If a new drug was found that remodelled bone, restored X-ray appearances to normal and cured symptoms this would lead to widespread acceptance that the drug worked. However the question would still remain about long term effectiveness and safety, issues that would inevitably limit its use. The true effectiveness of treatments can only be evaluated by controlled clinical trials, when the natural history of the disease in a control group is compared to the course of the disease in a treated group. There has been one well organised trial, the PRISM study that demonstrated the effectiveness of bisphosphonate treatment in reducing pain. Although this represents an optimistic finding the study failed to reach a conclusion on long term effects of treatment.

Natural history is a major compounding factor as it is so variable and only partly understood. Different patterns of bone involvement and varied levels of bone turnover lead to diverse symptoms across a range of patients. In addition there are very different long term complications including secondary arthritis, fracture, spinal stenosis, paraparesis, facial disfigurement and deafness. As any one complication has a relatively low incidence the use of both quantitative and qualitative assessment regarding these complications is problematic. Furthermore, even if studies can demonstrate an effect in a set of "study" patients, those in the "real world" provide an even greater challenge as they frequently have other co-existing conditions. One solution to this could lie in the improved description of the natural history of a specific subgroup such as the presence of Paget's in the femur with its risk of fracture and hip arthritis. By focussing on a discrete area of interest it may be easier to assess the effects of any intervention on natural history.

A further problem with respect to Paget's disease is time scale. As it is a chronic condition that is initially silent effective intervention may need to be early at a time when there is a possibility of altering the natural history. This raises the question about the need for a screening process to identify patients. In addition, any study may need to span many years which raises challenging issues regarding ongoing contact with patients and ongoing financial costs.

Finally it is always a challenge to power studies adequately to demonstrate effectiveness and if a drug has a smaller effect on the disease process greater numbers will be required to power a study. It is important to avoid making a type one error and not assess an ineffective drug as effective; paradoxically demonstrating a drug is definitely not effective is very demanding. It is also vital to avoid making a type two error and abandoning an effective drug because there have been insufficient numbers to power the study.

Are there any solutions to these problems to ensure future progress in the management of Paget's disease? Multi centred trials would provide the opportunity for greater recruitment to studies but these require dedicated co-ordination and must also consider the added administrative challenge of the regulatory process of research governance and ethics approval.

From a patient perspective, internet use may offer opportunities that were not previously available. It could enfranchise patients to recruit themselves into studies anywhere around the world. It would at least allow key subgroups to be identified, the natural history documented and better recruitment into future controlled trials. If patients could drive their own study using the internet they may help break out of the present quandary...what happens if we actively treat in the long term?