

Patient Selection and Achieving Best Outcomes from Bisphosphonate Treatment Options

a report by

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Osteoporosis fractures continue to represent a major health burden. Often described as the 'silent disease', it presents one of the most serious disorders among the aged population. Indeed, osteoporosis is estimated to affect in excess of 30 million – primarily female – people worldwide. The effects of increasingly porous and fragile bones are intrinsically linked with heightened levels of morbidity and mortality in the older population.

Certainly, women remain at the highest risk of developing the disease, primarily due to the decrease in oestrogen, a process that is particularly evident following the menopause. With nine out of 10 fractures occurring in people over the age of 50 – and over 80% of these women – the problem of osteoporosis remains considerable.

Key in the development of osteoporosis is the effect on the dynamics of the basic multicellular unit (BMU) and the subsequent impact on boundary modelling. In a healthy adult skeleton, the formation – and removal – of bone is regulated, with the BMU responsible for the regeneration and bone maintenance. Indeed, the bone is continuously undergoing a process of destruction and reconstruction, formation and absorption. This balanced process involves two specialised cells: osteoclasts and osteoblasts. Bone reabsorption is conducted by osteoclasts, whereas osteoblasts are responsibly for the construction of new bone. Once bones are formed, their shape and structure are continually renovated and modified by two processes, modelling and remodelling, resulting in the replacement of old bone by new bone. Modelling is predominant during an individual's growth. Conversely, when more bone is destroyed than formed, bone loss occurs and bone diseases such as osteoporosis may develop.

A number of factors are linked to the regulation of bone remodelling. Indeed, in osteoporosis, following a certain age, the two processes are uncoupled. Particularly following the menopause, the process of bone immobilising increases very rapidly. With this high bone turnover, the uncoupling of bone formation and absorption is amplified tremendously

by the high bone turnover; the number of sinews rise by a factor of 10.

Optimising Patient Selection

Critical in the treatment of osteoporosis is patient selection, and this very process has experienced considerable change. Until recently, clinical diagnosis of osteoporosis had been primarily based on a bone mineral density (BMD) reading.

However, another approach has more recently come to the fore. It is now evident that the risk of fracture is not linked exclusively to BMD, but is shaped and governed by other variable factors. Medications, lifestyle and history of fracture – all independent risk factors from BMD – have to be taken into account when a clinician targets treatments for specific patients who are at high-risk of fracture. This newer approach builds a far more complex and detailed understanding, and should provide far greater insight and accuracy and effectiveness for managing osteoporosis.

Patient identification therefore remains key: it is important to determine treatment options by selecting patients who are at very high risk.

In terms of treatments, several types of medication are available to reduce the rate of bone loss, and subsequently increase bone density. Primarily these work by means of lessening bone breakdown (anti-resorptive agents) or by stimulating the formation of new bone (anabolic agents). Whilst a bolus of vitamin D remains important, hormone replacement therapy (HRT) – normally using drugs to restore oestrogen levels that decrease after menopause – has been a standard treatment. However, concerns relating to long-term use of HRT have emerged, with possible links to breast cancer and heart disease. Alternatively, bisphosphonates, which attach to minerals, primarily calcium, in the bone have more recently come to the fore. Ingested by the osteoclasts, bisphosphonates have been demonstrated to decrease their effects, so less bone is broken down and thus bone density does not experience such decline.

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The Role of Bisphosphonates

Bisphosphonates have been found to effect the formation of farnesyl diphosphate synthase (FPP), which inhibits the production of the lipid FPP – key in the biosynthetic mevalonate pathway. There exist minor differences between bisphosphonates with regard to their strength of action, their potency, inhibiting the FPPS enzyme and their affinity towards hydroxylapatite. It is important is that the triphenylphosphine is able to work for a long period of time. With bisphosphonates – particularly those with high affinity – it is clear that they can effectively inhibit bone absorption for a prolonged period of time.

However, it is also clear that daily dosing with bisphosphonates may bring negative pharmacological implications. Acidity – generated by osteoclasts – is a prerequisite for the bisphosphonate to get deep inside the osteoclast. However, should a tablet not be consumed correctly – perhaps not immediately reaching the stomach – this may trigger gastrointestinal (GI) implications, for example irritation of the oesophagus or the stomach. This is a most notable side effect and, thus, with the risk of GI irritation – along with the presence of other possible obstacles – as clinicians we cannot be sure that we are achieving consistent patient adherence with daily therapy. To avoid these problems, it is important that the patient stay upright for an hour after taking the medication to prevent the drug from flowing to the upper part of the stomach and back into the oesophagus.

As a result, such daily bisphosphonate treatment should be taken under fasting conditions, whilst the patient must also remain upright for about one hour following the administration of the medication. Patients must also drink a large amount of water to ensure that the tablet goes straight to the stomach and is dissolved. In summary, the administration of once-daily bisphosphonates has proved troublesome, and – even if patients follow relevant precautions – complications may still be evident.

Intermittent Oral and Intravenous Dosing

From studying the pharmacology of the bisphosphonate, it is possible to achieve significantly improved adherence whilst minimising possible side effects through the application of less frequent dosing. This entails consuming a higher bisphosphonate dose at less regular intervals – for example, once per week, or indeed once per month. The latter has proved to demonstrate a high degree of efficacy whilst also proving highly convenient for the patient.

Furthermore, we know that by changing the dosage interval we can significantly increase adherence to therapy and thus improve the treatment outcome. For example, the adherence of drugs is often notably less in reality than demonstrated in clinical trials, as patients may not be administering the treatment correctly – for instance, not remaining upright, or fasting for the specified period. As a result, the treatment outcomes may be considerably reduced. Indeed, recent research has concluded that the number of non-responsive patients may be significantly higher on actual treatment regimes compared with those monitored under trial conditions. Key to overcoming this is the convenience of the therapy – this impacts adherence. Therefore, not just for patient convenience, but also for bisphosphonate adherence, it is important that dosing intervals be longer and the dosing less frequent. In this respect, once-monthly dosing with ibandronate is proving to give rise to better patient outcomes than achieved by daily-dosing regimes.

Subsequently, once-monthly bisphosphonate treatment regimes have provided a key solution to this problem. Whilst there may be circumstances where daily or weekly administration may still best suit some patient populations, personal experience suggests that an overwhelmingly large proportion of patients are keen – and best suited – to pursue this monthly plan.

Alternatively, bisphosphonates may also be delivered intravenously, a method that may be used in patients unable to take oral therapy for various reasons – perhaps due to being bed-ridden and thus unable to swallow the tablets, due to the presence of particular GI conditions, or perhaps due to polypharmacy. In such circumstances it is imperative to have an alternative option for administration.

Conclusion

Clearly, there have been major advances in the treatment of osteoporosis, from patient selection to treatment. In the former, reliance on factors such as BMD for assessment of fracture risk has eroded, and has subsequently been replaced by a more sophisticated model that places emphasis on variables that deliver a truer assessment of patients' risk of fracture. In terms of prevention and treatment, bisphosphonates have proven in clinical trials to be an efficacious therapy. However, limitations and suboptimal adherence have placed emphasis on the need for better dosing regimes. As a result, clinical trials have demonstrated that less frequent, particularly once-monthly, bisphosphonates may permit improved anti-absorption activities whilst reducing the chances of GI complications, culminating in the better serving of patient needs both in terms of convenience and in terms of what may be achieved by the treatment. ■