Institution: University of Sheffield

Unit of Assessment: 1 - Clinical Medicine

Title of case study: Health and economic impact of a new drug intervention for osteoporosis

1. Summary of the impact

Research at the University of Sheffield has demonstrated that zoledronic acid is an effective and safe treatment for osteoporosis. It resulted in a new drug intervention (Aclasta/Reclast) which has been licensed in more than 100 countries and shows increased positive outcomes for patients.

As a result of the licensing of the drug, clinical guidelines have changed globally. For patients, the drug provides a preferred method of treatment, evidenced in surveys which show the majority of patients preferred an annual infusion of zoledronic acid to the alternative, which is the standard treatment of weekly oral alendronate.

Industry has invested in research and development of the drug. Novartis has funded studies into the efficacy and safety profile (up to 2012); in 2011, sales of Aclasta/Reclast were US$0.6 billion.

2. Underpinning research

Osteoporosis is a major public health problem; there are more than 230,000 osteoporosis-related fractures annually in the UK, 70,000 of which are hip fractures, and these figures are set to rise with the increase in the elderly population (www.nos.org.uk). Treatments are available that reduce the risk of fracture; the most commonly-used treatments are bisphosphonates. Zoledronic acid is a bisphosphonate that can be given parenterally once a year and was licensed for use in men and women with osteoporosis in 2008.

Research at the University of Sheffield played a pioneering role in the development of the bisphosphonate drugs. Professor Graham Russell (Department of Human Metabolism, 1975 to 2000) made a major contribution to their early clinical development as well as the understanding of the mechanism of action of bisphosphonates at the cellular and molecular level which laid the scientific foundation for their current use. In a range of research projects, he studied amoebae (Dictyostelium discoideum) and immortalised macrophages (J774 cells) and showed that nitrogen-containing bisphosphonates induced apoptosis by inhibiting the mevalonate pathway and hence post-translational prenylation of GTP-binding proteins (inhibiting the enzyme farnesyl diphosphate synthase) and published this in 1998 (R1).

Professor Richard Eastell (Department of Human Metabolism, University of Sheffield, since 1995) developed assays for bone turnover markers, evaluated physical measurements of bone and developed methods for defining vertebral fractures. Sheffield was funded for this work by peer-review organisations. For example, the work on quantitative computed tomography was funded by the Medical Research Council (Biomarkers grant) and by Arthritis Research UK (project grant). The work on vertebral fracture definition was funded by the Medical Research Council (Fellowship) and Arthritis Research UK (Project grant).

Thus, Eastell was able to help design the HORIZON study in 2001 to assess the efficacy and safety of zoledronic acid in osteoporosis. This was a phase III clinical trial of zoledronic acid sponsored by Novartis and Sheffield was a study site. The drug was unique in that it was administered as a once a year infusion; the standard approach to giving bisphosphonates had been as daily or weekly tablets. The knowledge gained from experiments in Sheffield between 1993 and 2001 allowed Eastell, along with his fellow members of the trial steering committee (chairman Dr D Black), to ensure the following state of the art methods were included in the HORIZON trial: bone turnover marker response (R2), bone mineral density response (R3), quantitative computed tomography of hip and spine response (R4) and the effect of the drug on fracture risk (R5).

Findings of the HORIZON study showed that the drug reduced vertebral fractures by 70%, hip fractures by 41% and non-vertebral fractures by 25%. Statistical analysis by Richard Jacques (School of Health and Related Research, University of Sheffield, since 2008) allowed a better understanding of the link between change in bone mineral density, bone turnover markers and fracture risk (R6), and this work provides a target for response to zoledronic acid in the individual patient.

3. References to the research

University of Sheffield researchers in **bold**

R1. Luckman, S. P., Coxon, F. P., Ebetino, F. H., **Russell, R. G.,** and Rogers, M. J. (1998) Heterocycle-containing bisphosphonates cause apoptosis and inhibit bone resorption by preventing protein prenylation: evidence from structure-activity relationships in J774 macrophages. *J.Bone Miner.Res.* **13**, 1668-1678 doi: 10.1359/jbmr.1998.13.11.1668

R2. Delmas, P. D., Munoz, F., Black, D. M., Cosman, F., Boonen, S., Watts, N. B., Kendler, D., Eriksen, E. F., Mesenbrink, P. G., and **Eastell, R**. (2009) Effects of yearly zoledronic acid 5 mg on bone turnover markers and relation of PINP with fracture reduction in postmenopausal women with osteoporosis. *J.Bone Miner.Res.* **24**, 1544-1551 doi: 10.1359/jbmr.090310

R3. **Eastell, R**., Black, D. M., Boonen, S., Adami, S., Felsenberg, D., Lippuner, K., Cummings, S. R., Delmas, P. D., Palermo, L., Mesenbrink, P., and Cauley, J. A. (2009) Effect of once-yearly zoledronic acid five milligrams on fracture risk and change in femoral neck bone mineral density. *J.Clin.Endocrinol.Metab* **94**, 3215-3225 doi: 10.1210/jc.2008-2765

R4. **Eastell, R**., Lang, T., Boonen, S., Cummings, S., Delmas, P. D., Cauley, J. A., Horowitz, Z., Kerzberg, E., Bianchi, G., Kendler, D., Leung, P., Man, Z., Mesenbrink, P., Eriksen, E. F., and Black, D. M. (2010) Effect of once-yearly zoledronic acid on the spine and hip as measured by quantitative computed tomography: results of the HORIZON Pivotal Fracture Trial. *Osteoporos.Int.* **21**, 1277-1285 doi: 10.1007/s00198-009-1077-9

R5. Black, D. M., Delmas, P. D., **Eastell, R**., Reid, I. R., Boonen, S., Cauley, J. A., Cosman, F., Lakatos, P., Leung, P. C., Man, Z., Mautalen, C., Mesenbrink, P., Hu, H., Caminis, J., Tong, K., Rosario-Jansen, T., Krasnow, J., Hue, T. F., Sellmeyer, D., Eriksen, E. F., and Cummings, S. R. (2007) Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N.Engl.J.Med.* **356**, 1809-1822 doi: 10.1056/NEJMoa067312

R6. Jacques, R. M., Boonen, S., Cosman, F., Reid, I. R., Bauer, D. C., Black, D. M., and **Eastell, R.** (2012) Relationship of changes in total hip bone mineral density to vertebral and nonvertebral fracture risk in women with postmenopausal osteoporosis treated with once-yearly zoledronic acid 5 mg: the HORIZON-Pivotal Fracture Trial (PFT). *J.Bone Miner.Res.* **27**, 1627-1634 doi: 10.1002/jbmr.1644

4. Details of the impact

HEALTHCARE IMPACT

This research has led to a new drug intervention for osteoporosis. Through our research, we demonstrated that Zoledronic acid is effective and it was subsequently licensed by the European Medicines Agency in 2007 [S1].

The drug was approved based on the phase III clinical trial studies such as the HORIZON trial. It was approved in women [S2, S3], men, people with hip fractures [S4], and with glucocorticoid-induced osteoporosis. As a result of this research, the drug has been licensed in over 100 countries and more than 2 million doses of the drugs have been administered since 2007.

The main beneficiaries of this research are patients with osteoporosis; they receive a well-tolerated and simple to administer treatment that they prefer to the alternative (oral alendronate) and have a large reduction in their risk of fracture (by 70% for vertebral fracture).

The development of zoledronic acid as a treatment for osteoporosis is original as it is the first (and only) treatment that can be administered as infrequently as once a year. This contribution allowed for the successful development of this drug by conducting a well-designed trial, and allows a clear understanding of the mechanism of action of the drug at the molecular and whole body level. The Global Program Head at Novartis has recognised the part played by the University of Sheffield in both developing the use of zoledronic acid for treatment of osteoporosis, as well as sales worth $0.6bn (S3) in 2011 [S5].

Clinical guidelines have changed as a result of the drug being licenced. The Scottish Medicines Consortium has recommended that this treatment should be used in patients who are unsuitable for or unable to tolerate oral treatment options for osteoporosis [S6]. The treatment has not yet been considered by NICE, although treatments for Osteoporosis are currently under review by NICE.

The treatment has been included in international guidelines. Expertise gained through our research has been called upon to inform international practice which recommends zoledronic acid as best practice.

Eastell was an advisor on the Endocrine Society panel during 2009-2012 [S7] in the formation of new international guidelines for male osteoporosis, which include the recommendation to use zoledronic acid (S5). The treatment has also been included in the International Osteoporosis Foundation (IOF) guidelines for glucocorticoid-induced osteoporosis and three Sheffield professors were on that panel during 2009-2012 (John Kanis, Eugene McCloskey and Eastell).

The use of bone mineral density to identify response in the individual patient was the basis for a guideline from the IOF, and Eastell and Kanis were two of the members of the panel [S8]. Monitoring of zoledronic acid with bone turnover markers and bone mineral density was described in guidelines from the IOF on which Kanis and Eastell were members.

The user experience has improved. According to research into patient experience conducted in the USA, 66-79% of patients preferred an annual infusion of ZA to weekly oral alendronate [S9], the standard treatment of osteoporosis currently recommended by NICE.

ECONOMIC IMPACT

The costs of treatment have changed as a result of research-led changes in practice. The treatment is the most cost-effective for postmenopausal osteoporosis (Scottish Medicines Consortium). Research conducted in France found that, for example, treatment with zoledronic acid cost €1,216 per hip fracture avoided compared to €1,323 for standard treatment [S10].

Industry has invested in research and development. Novartis has funded studies into the efficacy and safety profile through establishing clinical trials of more than 11,000 patients for up to 9 years.

5. Sources to corroborate the impact

S1. European Medicines Agency European public assessment report variation WC500020936 for Aclasta (zoledronic acid) (http://tinyurl.com/o6qbwkd)

S2. FDA Label change for Reclast (zoledronic acid) approving it fo use in treatment of osteoporosis in postmenopausal women and treatment of Paget's disease of bone in men and women (http://tinyurl.com/psgsqw9).

S3. Press release gives details of approval of drug for use in men (http://tinyurl.com/lxskhth).

S4. Gives details of approval for drug to be used with hip fractures (http://tinyurl.com/kqrs7yn).

S5. E-mail from Global Program Head, Novartis, available on file.

S6. The Scottish Medicines Consortium recommendation for use of Aclasta (http://tinyurl.com/q5klw5n).

S7. Page 5, recommendation 3.2 corroborates inclusion of zoledronic acid as a recommended treatment (http://tinyurl.com/m5fkuog).

S8. Vasikaran, S., Eastell, R., Bruyere, O., Foldes, A. J., Garnero, P., Griesmacher, A., McClung, M., Morris, H. A., Silverman, S., Trenti, T., Wahl, D. A., Cooper, C., and Kanis, J. A. (2011) Markers of bone turnover for the prediction of fracture risk and monitoring of osteoporosis treatment: a need for international reference standards. Osteoporos.Int. 22, 391-420 doi: 10.1007/s00198-010-1501-1

S9. McClung, M., Recker, R., Miller, P., Fiske, D., Minkoff, J., Kriegman, A., Zhou, W., Adera, M., and Davis, J. (2007) Intravenous zoledronic acid 5 mg in the treatment of postmenopausal women with low bone density previously treated with alendronate. Bone 41, 122-128 doi: 10.1016/j.bone.2007.03.011

S10. Fardellone, P., Cortet, B., Legrand, E., Bresse, X., Bisot-Locard, S., Vigneron, A. M., and Beresniak, A. (2010) Cost-effectiveness model of using zoledronic acid once a year versus current treatment strategies in postmenopausal osteoporosis. Joint Bone Spine 77, 53-57 doi: 10.1016/j.jbspin.2009.04.009