Clinical Paper

Real World Experience of Denosumab Treatment in the Belfast Osteoporosis Service

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ABSTRACT

Osteoporosis is a significant global health and economic burden associated with bone fracture, morbidity and mortality. Denosumab, a novel human monoclonal antibody second-line treatment, inhibits osteoclast-mediated bone resorption and increases bone mineral density (BMD). Treatment achieves reductions in vertebral, non-vertebral and hip fracture risk. We undertook a service evaluation to review clinical outcomes of patients treated with denosumab in an osteoporosis department that provides regional services.

We identified 529 patients (95% female; mean age 72.8 years; 35-98 years), who had at least one dose of denosumab administered for the treatment of osteoporosis. The mean number of denosumab doses administered was 4.9 (range: 1 to 12). 330/529 patients had completed a baseline and post-treatment bone densitometry scan (DXA).

The mean observed BMD change at around 18 months at the lumbar spine was +8.4% and at the hip was +3.5%. While the majority have transitioned to shared care administration of treatment within primary care (53%), 20% continue to attend hospital clinics to receive treatment. During follow-up, there were 66 deaths (12%). 15% switched to an alternative treatment or were discharged.

This retrospective cohort study demonstrates the clinical effectiveness of denosumab in improving bone mineral density in a real life setting in an ageing, co-morbid population. There has been recent progress with adoption of shared care administration in primary care. As part of a quality improvement programme we have recently developed a dedicated denosumab database and day-case treatment clinic for those receiving treatment in secondary care.

INTRODUCTION

Osteoporosis is a public health challenge, characterised by low bone mass and fragility fracture. There are approximately half a million fragility fractures in the United Kingdom each year.[1] It is estimated that 1 in 2 women and 1 in 5 men over the age of 50 years are affected with a direct cost of fragility fractures of £4.3 billion per year in the UK.[1] Common sites of fragility fracture include the vertebral bodies, distal radius, proximal humerus, pelvis and proximal femur.[2] Several effective drug therapies are available for fracture prevention and are associated with improvements in bone mineral density (BMD) on bone densitometry (DXA).[2,3]

National guidelines recommend first-line therapy with oral bisphosphonates, which are associated with three-year relative risk reductions in fracture ranging 41-47%.[2-5] Limitations of oral bisphosphonate therapy, including upper gastrointestinal side-effects, poor medication persistence and contraindications in advanced chronic kidney disease impact clinical effectiveness.[2,3]

Denosumab (Prolia®) is a human monoclonal antibody that binds to a receptor activator of nuclear factor-ϰB ligand (RANKL), preventing activation of its receptor, RANK, on the surface of osteoclasts.[6] Denosumab acts as an anti-resorptive treatment by decreasing bone resorption in cortical and trabecular bone through inhibiting osteoclast formation and survival.[6] Denosumab is licensed for primary and secondary prevention of fragility fracture in postmenopausal women and in men.[6] Indications include post-menopausal osteoporosis, glucocorticoid induced osteoporosis, in chronic kidney disease and for those intolerant to bisphosphonates. Treatment is administered twice yearly by subcutaneous injection.[7]

Treatment with denosumab for 3 years significantly reduces the risk of fracture at vertebral (68%), non-vertebral (20%) and hip fracture (40%) sites, compared with placebo. The benefits of denosumab were first demonstrated in the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) study.[8] This large randomised controlled clinical trial, in 7,808 women aged 60-91 years, was subsequently extended with open label treatment with gains of BMD steadily accruing for up to 10 years.[9]

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We introduced denosumab into our osteoporosis clinic following NICE Technology appraisal guidance approval. We recently reviewed clinical outcomes in our service to assess the effectiveness and outcomes of denosumab treatment. [4]

METHODS

Patients were identified through a prospectively updated Microsoft Excel® denosumab database kept by the Osteoporosis nursing team.

DEMOGRAPHICS

Musgrave Park Hospital is a tertiary referral hospital that provides osteoporosis services for the greater Belfast Area and a proportion of regional osteoporosis services for Northern Ireland. Patients are referred by general practitioners for assessment and diagnosis by DXA scanning. Patients are also directly recruited from fracture clinics following fragility fracture.

PARTICIPANTS

A retrospective examination of medical records of patients attending Musgrave Park Hospital was performed for all patients who had commenced denosumab between March 2012 and June 2017.

We collected data on demographics, gender, age, renal function, vitamin D status and outcome at last date of follow-up. Relevant clinical demographics for each patient were identified using a number of regional Electronic Records systems, (Orion Health – Concerto; Sectra – PACS Workstation IDS7). Documentation from attendances and correspondence with patient's primary healthcare provider and location of administration was also recorded.

BONE DENSITOMETRY SCANNING (DXA).

BMD assessment was undertaken with the GE Lunar iDXA scanner, which has a reported least significant change of 0.033 g/cm^2. World Health Organisation (WHO) diagnostic criteria for osteoporosis were used.[10]

OUTCOMES

Our primary outcome was to determine the rates of denosumab usage within the clinical service and to assess the percentage change in BMD at hip and lumbar spine sites for those who had a follow-up DXA study. We identified all patients who died during follow-up and ascertained their cause of death by reviewing the electronic medical record. Reasons for drug discontinuation and fracture outcomes following denosumab withdrawal were reviewed. We explored rates of adoption of administration of denosumab within primary care.

STATISTICAL METHODS

All results were analysed using GraphPad Prism 7.0b and continuous data was presented as median and range. Results were considered significant if the *p* value was <0.05. The Mann-Whitney U test was used for non-Parametric data.

RESULTS

529 individuals (aged 35-98 years) received at least one dose of denosumab 60 mg (Table 1). A majority (95%) were female in keeping with NICE recommendations. The mean age of the study population was 72.8 years. Males were significantly younger at 62.8 years compared with females (73.3 years, p<0.0001). Clinical data was available during a mean follow-up period of 2.8 years (range 17 days-6.5 years). Individuals received a mean number of 5 doses during treatment (range 1-12 doses). The median eGFR for the series was >60 mls/min; range 5-60 mls/min. Mean Vitamin D stores were replete at 76.4 nmol/l.
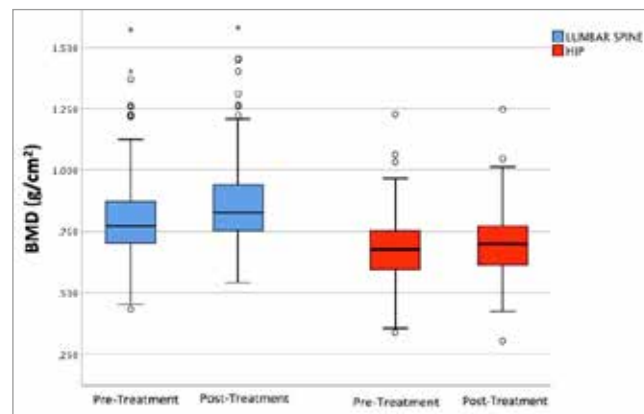

Fig 1. Absolute change in bone mineral density (BMD) at lumbar spine and hip sites

Baseline DXA scans showed a mean T-score of -2.6 (total hip) and -3.0 (lumbar spine) sites. 53% of subjects had concordant T-scores for both hip and spine sites within the osteoporosis range according to WHO classification. Some individuals had T-scores within the osteoporosis range at hip (70/529) or spine (174/529) sites alone. A smaller number with fragility fractures and osteopenia were noted within the cohort (n=62).

334/529 patients had completed a follow-up DXA during denosumab therapy at a mean duration of around 18 months of treatment. There were significant increases in BMD at both spine and hip sites, p <0.0001 (Fig 1). The mean BMD change at the lumbar spine was 0.063 g/cm^2, representing a 8.4% gain (range -0.103 to 0.417 g/cm^2) (Fig 2.). Hip BMD increased
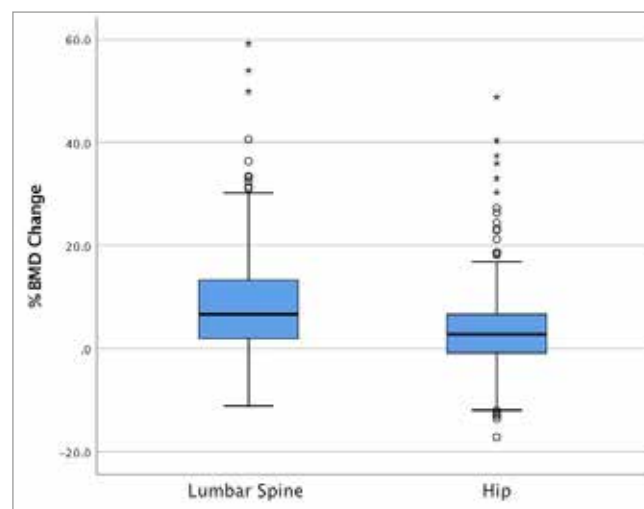

Fig 2. Percent change in bone mineral density (BMD) at lumbar spine and hip sites

Table 1.

Patient Demographics
Statistically significant difference, (p<0.0001); Mann-Whitney U Test.

Gender			
	Male	Female	
N (%)	27 (5.1%)	502 (94.9%)	
Age at first dose (years)			
	Mean	Median	Range
Total	72.8	74	35 – 98
Male	62.8*	63	35 – 88
Female	73.3*	74	35 – 98
Duration of follow-up			
Total (days)	1028	925	17 – 2383
Baseline eGFR (mLs/min)			
Total (n=529)	56.5	60	5 – 60
Male (n=27)	54.7	60	25 – 60
Female (n=502)	56.5	60	5 – 60
Baseline Vitamin D (nmol/L)			
Total	76.4	74	20 – 139
Male	79.4	74	
Female	75.3	74	
Baseline T Scores (S.D.)			
Lumbar Spine (Total; n=528)	-3.0	-3.2	-5.7 to 3.5
Male (n=26)	-2.6	-2.7	-5.2 to 3.0
Female (n=502)	-3.0	-3.2	-5.7 to 3.5
Hip (Total; n=509)	-2.6	-2.6	-5.4 to 3.1
Male (n=27)	-2.4	-2.4	-4.3 to 1.2
Female (n=482)	-2.7	-2.7	-5.4 to 3.1
Baseline BMD – Patients with paired pre- and post-Treatment DXA data (T-score S.D.)			
Lumbar Spine (Total; n=334)	0.795	0.772	0.432 - 1.572
Male (n=16)	0.903	0.845	0.551 - 1.572
Female (n=318)	0.790	0.771	0.432 - 1.403
Hip (Total; n=317)	0.681	0.676	0.338 - 1.228
Male (n=16)	0.809	0.816	0.523 - 1.228
Female (n=301)	0.674	0.667	0.338 - 1.033
Delivered doses (Denosumab)			
Total (n=340)	5	4	1 – 12
Male (n=16)	5	5	2 – 9
Female (n=324)	5	4	1 – 12

by 0.02 g/cm^2, representing a 3.5% gain (range: -0.107 to 0.214 g/cm^2). As expected, the absolute and percentage BMD change was significantly higher at spine than hip sites, (p<0.0001). 121 patients (36.3%), experienced net BMD losses at one or more sites; lumbar spine (n=29; 8.7%), hip (n=73; 21.9%), both (n=19, 5.7%). Exclusion of 'non-responders' from analyses resulted in more pronounced BMD gains at the lumbar spine, (Mean gain of 11.1%; p<0.0001), and at the hip, (Mean gain of 6.8%; p<0.0001).

A small number of men (n=27), who were unable to tolerate or were unsuitable for alternative second line treatment options, were treated with denosumab. Indications for denosumab in men included oesophagitis or Barrett's oesophagus (n=7), chronic kidney disease (n=5), and severe osteoporosis requiring sequential treatment (n=5). There was an absolute BMD gain at the lumbar spine and hip in males, (+ 0.093 g/cm^2 and + 0.014 g/cm^2), and females, (+ 0.053 g/cm^2 and + 0.0185g/cm^2). Neither observed difference between genders at lumbar spine, (p=0.086), or hip, (p=0.168), met statistical significance. Men presented with co-morbidities including difficult asthma, multiple sclerosis, prostate cancer, coeliac disease, sarcoidosis, hypogonadism, COPD and prior history of renal transplantation.

We examined the denosumab treatment effect stratified by age. Patients were divided into five groups, (<60; 60-69; 70-79; 80-89; 90+). Non-parametric analyses, (Krushkal-Wallis), were used to examine the difference between group medians. There were insufficient numbers of male patients to stratify by age and make a robust analysis. There were no significant differences between groups amongst female patients at lumbar spine, (p=0.207), or hip, (p=0.625). Despite the absence of statistical significance, there appeared to be an age related decreasing biological gradient in BMD change at lumbar spine from younger to older female patients: <60: +0.062 g/cm^2; 60-69: +0.063 g/cm^2; 70-79: +0.053 g/cm^2; 80-89: +0.0405 g/cm^2; 90+: +0.037 g/cm^2. There was a significant difference when treatment effect at lumbar spine in female patients was stratified by age <80 years, (+ 0.059 g/cm^2), and 80+ years, (+ 0.041 g/cm^2); p=0.046. This was not observed at the hip in either case.

The effect of chronic kidney disease on BMD was reviewed. There were no significant differences between BMD gain at either the lumbar spine, (+ 0.040 g/cm^2 vs. + 0.055 g/cm^2; p=0.101), or hip, (+0.0175 g/ g/cm^2 vs. +0.019 g/ g/cm^2; p=0.95), or between patients with CKD and without CKD. Spearman's Rank Correlation was used to assess the relationship between these data. No significant correlation was found linking age, vitamin D level or eGFR to BMD change at the lumbar spine or hip.

We explored outcomes of transition to shared care administration of treatment by the primary care provider as per regional guidelines. While a majority 281/529 (53%) transitioned to primary care administration of treatment, 104/529 (20%) continued to attend hospital clinics for treatment. 43/529 (8%) discontinued denosumab or switched treatment to an alternative treatment and 35/529 (7%) were discharged from follow-up, often due to advanced frailty or non-attendance. In most cases drug discontinuation was agreed after 1 or 2 doses. Common reasons for discontinuing treatment were failure to attend for treatment (n=5), loss of BMD or new fracture (n=2), respiratory or urinary infection (n=5), skin rash (n=5), other side-effects (n=11), completion of course (n=3), switch to other parenteral treatments (n=5), or patient concern/non-specified (n=7). Of those that discontinued denosumab treatment 15/43 sustained a new fracture, 8/15 of which were vertebral fractures (Fig 3). 27/43 remained free of further fractures. We observed relatively stable BMD at latest follow-up compared with pre-treatment baseline DXA with a mean increase in BMD at the lumbar spine of 0.049 g/cm^2 (-0.027g/cm^2 to 0.176 g/cm^2) and hip BMD at -0.001 g/cm^2 (-0.107 to 0.086 g/cm^2).
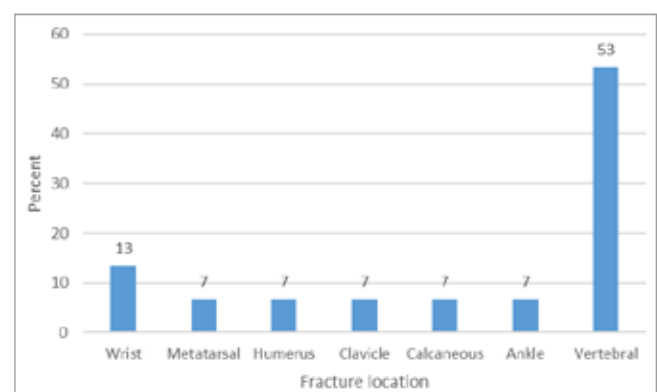

Fig 3. Location of fracture events following denosumab withdrawal

Most of the cohort were elderly with 18% between 70-74 years, and 48% were aged 75 years or older. 66/529 (12%) died during follow-up while being treated for osteoporosis. The mean age at death was 79.9 years (7 males, 59 females). Of those with a medically certified cause of death listed on the ECR, there were 26 cases of pneumonia/respiratory infection, 10 with various cancer conditions, 5 with chronic lung disease, 6 with cardiovascular disease, 3 with urosepsis. Other medically certified causes of death included dementia, and cerebrovascular disease (Fig 4).
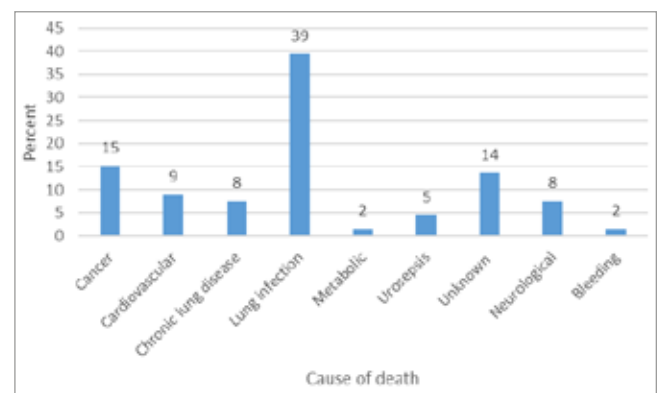

Fig 4. Medically certified causes of death within the series

Death occurred at mean of 2.3 years following initiation of treatment and at a mean of 1.7 years from administration of the last dose of treatment of denosumab. Several patients had

multiple co-morbidities, leading to cessation of treatment. We were unable to ascertain the cause of death in 9/66 of the series using the NI electronic care record (ECR).

DISCUSSION

Denosumab (Prolia®) is a novel anti-resorptive with proven anti-fracture efficacy.[6] Treatment is effective for the secondary prevention of osteoporotic fragility fractures and has particular utility for those who are unable to comply with the special instructions or tolerate treatment with first line bisphosphonates.[4]

In our retrospective cohort, we observed a mean increase in bone mineral density (BMD), at around 18 months, of 8.4% at the lumbar spine and by 3.5% at the hip. Our outcomes compare favorably with the FREEDOM trial where denosumab increased BMD by 9.2% at the lumbar spine and 6.0% at the total hip, compared with placebo after 36 months.[8] Like our cohort, BMD gains were noted at an early stage, at between 6 to 18 months. DXA is usually undertaken every two to three years to detect the least significant change (LSC) in bone mineral density. The LSC, is defined as the minimum change that must be exceeded before a change can be considered true with 95% confidence. For this reason, a threshold of around 4%, is generally considered to be a meaningful change in BMD during interval DXA monitoring.

Over a three-year period, the FREEDOM trial showed that increases in bone mineral density were associated with a reduction in the primary end point of risk of vertebral fracture, and secondary end points of non-vertebral, and hip fractures in women with osteoporosis. The present study was not designed to examine fracture outcomes, however it is anticipated that improvements in surrogate measures of BMD in our series might also be associated with fracture risk reduction.

Denosumab is well tolerated with an acceptable side effect and risk profile; it is also attractive due to the twice-yearly dosing schedule. All patients treated with denosumab are counselled regarding relevant drug related side-effects and symptoms, particularly to limit risk of hypocalcaemia, which is more likely in the setting of vitamin D deficiency or in advanced renal impairment[11]. In this series it was notable that a majority were Vitamin D replete and for those with Vitamin D insufficiency precautions around replacement of Vitamin D stores were observed carefully.

The FREEDOM trial included 3902 patients on denosumab treatment with a mean age of 72.3 years and with 31.7% of the series on active treatment over the age of 75 years. Serious adverse events such as infection were rare at 4.1% and no different from the placebo group. There has been a particular focus on counselling regarding the risk of osteonecrosis of the jaw and atypical fractures with anti-resorptive agents. The drug is contraindicated for individuals with latex allergy, as the needle cover of the pre-filled syringe contains a derivative of latex, which may cause allergic reactions[6]. As part of standard clinical care patients receive written information and counselling regarding the risks and benefits of treatment including urinary tract, upper respiratory tract infection, rash and eczema as common side effects ($\geq 1/100$ to $< 1/10$). Our series illustrates that respiratory tract infection and urosepsis are contributing factors to morbidity. It seems prudent to continue to adopt a cautious approach to patient selection, considering alternative agents for individuals predisposed to risk factors for lung or urinary infection where possible.

Our osteoporosis service has close links with the hip fracture service and ready access to those attending elderly care services within the Trust. However, the option of not prescribing denosumab therapy in very frail people, may be considered in some cases, balanced against the risks and benefits of treatment, particularly in those with limited life expectancy. Mortality rates within the FREEDOM trial were reported at 1.8% and were similar to placebo. Our series illustrates an ageing frail co-morbid population with a mortality rate of 12% at a mean age of 79.9 years. Comparative life expectancy rates within the Belfast District Council area at 65 years for females of 19.7 years and 18.2 years for men are noted in the general population.[12]

Denosumab is licensed in renal impairment, however, low bone mass is often multi-factorial with chronic kidney disease-metabolic disease being a major contributor that is managed within specialist nephrology clinics. We observed cautious use of denosumab in advanced CKD in our series. Evidence for use of denosumab in CKD is based on a small number of individuals with advanced CKD in the FREEDOM series. Individuals with severe renal impairment (creatinine clearance < 30 mL/min) or receiving dialysis are at greater risk of developing hypocalcaemia.[13] In this setting the risks of developing hypocalcaemia with increasing degree of renal impairment are higher. Adequate intake of calcium, vitamin D and regular monitoring of calcium is especially important.

We examined adoption rates for shared care administration of denosumab in primary care, to explore the effectiveness of regional shared care for administration in the community.[14] We have observed a slow but steady increase in uptake of primary care administration. We attribute this to increasing familiarity with the drug class and assurance that treatment has a favorable side-effect profile. There is further potential for left-shift to deliver services closer to home, as funding is in place for locally enhanced community administration.[15] Denosumab is not currently included within shared care guidelines or locally enhanced service administration to men in primary care. However, the treatment clearly has a role in male osteoporosis, as with other anti-osteoporosis treatments and we advocate that men should receive equitable access to existing treatment pathways.

We observed long-term tolerability of treatment, which was associated with improvements in BMD, in keeping with earlier series.[16] The FREEDOM extension trial was an open label study of all participants who completed the 3 year FREEDOM trial, without discontinuing treatment or missing more than one dose of investigational product, extending to 10 years of therapy.[9] Treatment was associated with low

fracture incidence, and a continuous increase, in BMD, without a plateau. In the long-term group, BMD increased from baseline by 21·7% at the lumbar spine, 9·2% at total hip and 9·0% at femoral neck.[9] In order to achieve these benefits, long-term follow-up strategies are needed to ensure regular administration of treatment and a structured process of follow-up. For this reason, we have developed a dedicated, password protected Microsoft Access® database to support the service.

Current guidelines recommend a treatment holiday from bisphosphonates after 5 to 10 years to limit the risk of rare anti-resorptive related side-effects.[2,3] Denosumab, in contrast has a short off-set of action and treatment discontinuation is associated with rapid loss of bone density with the potential risk of rebound fractures.[7,16,17] Generally, drug holidays are to be avoided and long-term denosumab treatment is required. Some patients may discontinue treatment either due to side-effects, ineffectiveness or intercurrent illness.[19-21] While a majority did not experience a subsequent fracture, 8/15 who did fracture in our series, had a vertebral fracture, which is a potential risk following treatment cessation. When a decision is taken to discontinue denosumab, alternative sequential treatment, either in the form of oral or intravenous bisphosphonate can be considered in order to preserve gains in BMD and to retain anti-fracture efficacy. This is an important aspect of care that should be highlighted during patient counselling during treatment.

Over the course of the past 6 years, due to increasing demands, we have introduced a series of service improvement measures. These have included template letters to highlight the availability of locally enhanced service payments for primary care administration and development of a dedicated Microsoft Access database to track patients commencing treatment and under follow-up in secondary care. We have also developed a new additional weekly dedicated day case denosumab treatment clinic to reduce pressures on outpatient clinic review appointments. We are optimistic that with increasing clinical engagement that we can positively impact fracture outcomes through co-ordinated care across primary and secondary care services.

In conclusion, this series further demonstrates the clinical effectiveness of denosumab in a real-life setting. Regular clinical assessment, including DXA imaging, and long-term clinical follow-up is required to assess response to treatment and to co-ordinate long-term care and transition between therapies. With the development of new treatment modalities such as this, we have demonstrated the need for ongoing service development. We remain optimistic of further left-shift for denosumab treatment in the community through promotion and adoption of shared care approaches.

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