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Does the Osteoporosis Dose of Denosumab Really Cause Clinically Significant Hypocalcaemia in CKD 4 and 5

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Author's contribution

Author PI designed the study, collected the data, reviewed the literature, performed the analysis and wrote the manuscript.

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ABSTRACT

Denosumab is a potent novel antiresorptive agent for treatment of osteoporosis with unique mechanism of action . It is a fully human monoclonal antibody to the receptor activator of nuclear factor-κB ligand (RANKL) that blocks its binding to RANK, inhibiting the development and activity of osteoclasts, decreasing bone resorption, and increasing bone density. Initially denosumab appeared particularly promising for patients with advanced stages of renal failure but over the past two years several publications questioned that, reporting adverse effects and especially severe hypocalcaemia.

Aim of the Study: to investigate further the effect of the osteoporosis dose of denosumab on serum calcium levels in patients with CKD 4 and CKD 5.

Methods: This retrospective outpatient study included 17 females with CKD 4 and 5 who received a single or a multiple (at 6 months intervals) 60-mg subcutaneous dose of denosumab. Adjusted serum Calcium was measured prior to the dose and at various points of time after that.

Results: Only two of the subjects developed clinically significant hypocalcaemia. Both of them were clearly inadequately supplemented with calcium and vitamin D.

Conclusion: The results from the current study along with a critical analysis of the previous publications reveal that the vast majority of the previous reports were based on inadequately supplemented with calcium and vitamin D patients and that severe hypocalcaemia is unlikely in appropriately supplemented subjects, especially in the CKD 4 subgroup. However, due to the scarcity of data further research is warranted,

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especially in the CKD 5 subgroup. In the mean time more cautious approach rather than a blanket ban on denosumab appears to be the most appropriate policy in these two populations.

Keywords: Denosumab; hypocalcaemia; osteoporosis; CKD 4/5.

1. INTRODUCTION

Denosumab is a potent novel antiresorptive agent [1] with a unique and well characterised mechanism of action. It is a fully human monoclonal antibody to the receptor activator of nuclear factor-κB ligand (RANKL) that blocks its binding to RANK, inhibiting the development and activity of osteoclasts, decreasing bone resorption, and increasing bone density. [2] In 2010 denosumab has been approved by FDA [3] and AMA for treatment of postmenopausal osteoporosis and skeletal-related events in patients with bone metastases from solid tumors [4,5] at a dose of 60 mg subcutaneously (s.c.) every six months and 120 mg s.c every four weeks, respectively.

According to the pre-registration trials [2] one of the main advantages of denosumab is its excellent renal safety profile which allows this medication to be prescribed even for patients with advanced stages of CKD. However, more recent publications questioned the initial findings, citing a number of cases in which denosumab has been associated with severe hypocalcaemia in patients with CKD 4 and 5. [6-11] Due to the scarcity of published clinical data so far there has been no consensus on the issue, with some authors claiming that in CKD 4 and 5 severe hypocalcaemia has been seen only in patients not adequately supplemented with Calcium and vitamin D [6], and others arguing that denosumab should not be used due to the risks of severe hypocalcaemia, difficulty in distinguishing low from high turnover bone states and lack of data on whether denosumab reduces the fragility fractures in the haemodialysis population [10].

The aim of the current study is to investigate further the effect of denosumab in CKD 4 and CKD 5 in terms of adverse effects and especially severe or symptomatic hypocalcaemia. Due to its limitations the current study cannot comment on the other concerns raised by the authors who did not support the use of denosumab in dialysis population [10].

2. METHODS

This retrospective outpatient study was conducted at the metabolic bone ward of Royal Liverpool University Hospital .The study included patients with Chronic kidney disease (CKD) 4 and 5 (they will be called subjects of the study for the purpose of this paper) who received a single or a multiple (at 6 months intervals) 60-mg subcutaneous dose of denosumab (Prolia; Amgen). We defined stages of kidney function based on the modified National Kidney Foundation classification of chronic kidney disease (K/DOQI Guidelines 2002) [12]. Based on this classification, stage 4 (severe decrease in estimated glomerular filtration rate (eGFR) is an eGFR between 15 to 29 mL/min/1.73m^2 and stage 5 is an eGFR < 15 mL/min/1.73m^2.

The subjects of the study were identified as follow: A computer search was performed by the laboratory information system (Telepath, Telepath Systems Ltd, UK) for the period 01.01.2008 - 05.02.2013) and all the patients with biochemistry request forms issued from

the metabolic bone day ward who had at least one eGFR result < 30 mL/min/1.73m^2 were identified. Of those the patients treated with denosumab were identified from the clinical letters to the GPs (stored on the departmental hard drive or on the hospital information system). The information regarding concomitant medication and adverse effects was obtained from the same source. The patients were followed every 3-4 months for a total duration ranging between 3 and 18 months (depending on the number of denosumab injections that they have received). Routine appointments with a medical doctor normally took place on the day of the injection and 3-4 months post dose .

Inclusion criteria: Females with osteoporosis or osteopenia according to WHO criteria (T-score ≤ -2.5 and (-1.0 and -2.5)[13] respectively, who received at least one dose of 60 mg s.c. denosumab as part of their treatment, eGFR < 30 mL/min/1.73m^2.

Exclusion criteria: Males, females who did not receive denosumab and females who had more than one eGFR result ≥ 30 mL/min/1.73m^2 during the course of treatment with denosumab.

The serum biochemistry results (albumin adjusted serum calcium (ACa), inorganic serum phosphate(iPh), Creatinine (Creat), eGFR ,alkaline phosphatase (ALP), albumin(Alb), intact parathyroid hormone (iPTH) , 25 Hydroxy Vitamin D (25(OH) vit D)) were obtained from the hospital information system (ICE, Sunquest Information Systems, Inc).

Analysers and methods used to measure the analytes. ***Calcium, iPh, albumin, creatinine, ALP***: (Roche Cobas c701, Roche Diagnostics). ***iPTH***: (Roche Cobas Modular E170, Noncompetitive biotin-streptavidin immunoassay with chemiluminescence detection, Roche Diagnostics). ***25 Hydroxy Vitamin D***: (HPLC-MS method, Waters Acquity chromatography / Waters Quatro Premier XE). ***eGFR*** was calculated using 4 variables MDRD formula. ACa was calculated from calcium(Ca) and albumin(Alb) serum concentrations using the following formula : ACa (mmol/L) = Ca(mmol/L) + 0.0133x(44.1-Alb(g/L)).

Since ACa, Serum Creat, iPh, albumin and ALP were routinely measured before the administration of Denosumab (ranging from 2 h to 16 days) these results were used as a baseline. The biochemistry parameters mentioned above were monitored at various points of time after that (3 to 210 days following denosumab). For the purpose of this study these results were grouped together into 7 time intervals as follow (day 3- day 14),(day15- day 30),(day 30-day 60),(day 60-day 90),(day 90- day 120),(day 120-day 150) , (day 150-day 210).

The baseline and the post dose results for each interval were checked for normality with Analyse-it software (Analyse-it Software Ltd., Leeds, UK) using Shapiro-Wilk test where they were sufficient data or frequency histogram with normal overlay.

25(OH) vitamin D levels were measured once or twice a year. iPTH results where available were also used as part of this study.

3. RESULTS

The initial screening identified 19 female subjects (age range 52 - 95 year) of which 2 were excluded as they had more than one eGFR result > 30 mL/min/1.73m^2. Of the remaining 17 subjects 12 had CKD 4 and 4 subjects had CKD 5. One subject had CKD 4 (patient number 17, Table 1) but later deteriorated into the CKD 5 range. This patient was

excluded from the statistical analysis for a different reason (noncompliance, discussed in detail below).

The normality analysis of the baseline and post dose samples revealed that most data were not normally distributed therefore in the statistical analysis median was used rather than mean.

ACa results: All subjects had their ACa measured before the administration of denosumab (range from 2 h to 16 days) and at varying points of time after that (3-210 days) (Table 1).All patients had normal pre-treatment ACa results (reference range (RR) 2.20-2.60 mmol/L). Following the administration of denosumab only 2 patients (patient under number 7 and 17, Table 1) developed clinical symptoms of hypocalcaemia and/or ACa levels < 1.95 mmol/L. Both patient were clearly inadequately supplemented and were excluded from the statistical analysis. Their cases will be discussed later in this paper. None of the remaining 15 patients (12 with CKD 4 and 3 with CKD 5, two of whom on haemodialysis(HD)) developed any symptoms of hypocalcaemia or serum levels of ACa <1.95 mmol/L at any point of time following the denosumab injection . Baseline ACa results were within the range 2.26-3.05 mmol/L, median 2.45 mmol/L (obtained from 25 results(n=25) as some subjects received more than one injection of denosumab(at 6 month interval) .Post denosumab ACa results were as follow: Day 3-14 (range 1.98-2.34, median 2.29), Day 15-30 (1.96 -2.43, median 2.13), day 30-60 (1.97-2.37, median 2.17), day 60-90 (2.04-2.67 , median 2.29), day 90-120 (2.21-2.58, median 2.32), day 120-150 (2.19-2.44, median 2.26), day 150-210 (2.32-3.05, median 2.49) (all results in mmol/L) .The change in calcium for the same period compared to the baseline was as follow : Day 3-14 (-0.75) - (+ 0.05), median (-0.51), day 15-30 , (0.12)–(-0.47) median (-0.38), day 30-60 (-0.93)– (+ 0.11), median (-0.34), day 60-90 , (-0.58)-(+0.12) , median (-0.16), day 90-120 , (-0.30) – (+ 0.11) median (-0.14), 120-150 , (-0.41) –(-0.05) median (-0.07) , day 150-210 (-0.40)-(+0.83) median (+0.02). (all results in mmol/L). **Inorganic Phosphate, ALP, Albumin** and **eGFR:** The same approach has been applied to those analytes (Table 2). **25(OH) vitamin D*:*** 14 out of the 15 patients had their 25(OH) vitamin D levels measured before the administration of denosumab. Of those nine had 25(OH) vitamin D > 50 nmol/L and four < 50 nmol/L. All four patients with 25 OH vitamin D < 50nmol/L were supplemented with alfacalcidol or colecalciferol prior to denosumab. One patient did not have 25 OH vitamin D measured. **iPTH:** iPTH was measured on 8 patients . Six of them met the KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD–MBD)[14] (In the current paper they will be referred to as KDIGO guidelines) targets for iPTH (within the reference range for CKD4 and within 2-9 times the upper limit of reference range for CKD5), one (on HD) did not and one patient with CKD 4 had iPTH above target prior to the first denosumab injection and within target prior to the second one. **Special cases: *1. Patient No7*** (Table 1). This was a 68 year old female HD patient with known serious compliance issues who received denosumab on two occasions . On both occasions she developed severe hypocalcaemia detected when she had a predialysis blood test 20 and 9 weeks after the first and the second injection of denosumab , respectively. On the first occasion she was asymptomatic and on the second one she was hospitalised for 24 hours and treated with IV Calcium gluconate and oral calcium and vitamin D supplementation as she had paraesthesia and prolonged QT interval on ECG. The patient reported serious compliance issues with her calcium and vitamin D supplementation after receiving denosumab which was supported by her erratic ACa results (Table 1). Two weeks post the second denosumab her ACa levels rose from 2.29mmol/L to 2.61mmol/L then decreased to 1.79 mmol/L seven weeks later. She was also known to have compliance issues and

several episodes of hypocalcaemia in the past. ***2. Patient No 21*** (Table 1) . This was a 90 year old female on HD who developed peripheral paraesthesia and severe hypocalcaemia of on day 12 following denosumab and was consequently hospitalised. Preclinic bloods of this patient appeared to meet KDIGO guidelines (ACa was 2.52 mmol/L, PTH 51.2 pmol/L and 25(OH) vit D 118 nmol/L). However the patient was not on any calcium or vitamin D supplementation prior to denosumab which is unusual for HD patients. This issue will be discussed in greater detail in the discussion section of this paper.

4. DISCUSSION

4.1 Limitations of the study

The study included relatively small number of subjects, especially in CKD 5 group. The data was collected retrospectively and might have been affected by inaccuracies in the patients' records. After the closure of the metabolic bone unit in 2012 the patients started to receive denosumab on one of the general medical ward but those who had their first denosumab on the new ward were not identified and included in the current study due to the limitations of the computer search. Therefore the current study may well have not included all consecutive patients with CKD 4 and 5 treated with denosumab on the ward. Adverse clinical reactions were recorded at a clinic appointment 3 months after the injection therefore the patients might not have been able to recall possible adverse effects and particularly mild ones. Due to some missing calcium data points, some asymptomatic, laboratory defined hypocalcaemia events may have been missed, especially in the first two weeks post dose.

In the past two years there has been a lot of debate whether the dose of denosumab used for treatment of osteoporosis (60 mg s.c. every 6 months) can cause clinically significant hypocalcaemia in patients with CKD4 and CKD 5. [2,6-11] (For the purpose of this study we defined the term "clinically significant hypocalcaemia" as symptomatic hypocalcaemia or ACa <1.90 mmol/L . This cut off was chosen because from our clinical experience above it patients are very unlikely do develop symptomatic hypocalcaemia). The debate has been hindered by the small number of cases with CKD 4 and 5 in which denosumab has been administered.

The initial analysis of data from the *FREEDOM study* (7808 postmenopausal women) did not find any significant hypocalcaemia (defined as ACa < 2.00 mmol/L at 6 months post dose).[2] All participants received daily supplements containing at least 1000 mg of calcium. Women with 25 (OH) vitamin D) < 30 nmol/L were excluded from the study and those above this level received at least 400 IU of vitamin D daily[2]. It should be noted that in this study, only 73 women had a calculated creatinine clearance 15 to 29 mL/min /1.73m^{2}and none had end-stage renal dysfunction (< 15 mL/min/1.73m^2) [11].

Table 1. ACa levels and change of ACa following denosumab (in mmol/L)

Patient number	Baseline eGFR	Baseline ACa RR(2.20-2.60)	Day 3-14 days	Day 15-30	Day 30-60	Day 60-90	Day 90-120	Day 120-150	Day 150-210
1	16	2.26			2.37	2.25	2.31		
2	28	2.40			2.20				
3*	29	2.42			2.10				2.51
	26	2.51					2.32		2.38
4	16	2.49				2.33			
5*	9	2.38			1.97		2.31		2.49
	7	2.49			2.26			2.44	
6*	6	2.33		1.97		2.04		2.26	3.05
	4	3.05	2.30		2.12				
7**	**21****	**2.43****					**2.18****	**1.79****	**2.29****
	9**	**2.29****	**2.61****			**1.79****			
8*	16	2.71			2.25				2.70
	13	2.70				2.53			2.58
	16	2.58	2.07		2.21	2.46			
9	17	2.47					2.58		2.40
10*	27	2.45				2.48			
	27	2.28	2.34						
11	20	2.62						2.19	2.32
12*	6	2.49	1.98		2.14		2.35		2.76
	4	2.76	2.28	2.29	2.03	2.18	2.46		
13*	18	2.37		1.96	2.03	2.08	2.21		2.55
	15	2.55		2.43		2.67			
14	24	2.43	2.32						
15	28	2.26			2.32				
16*	25	2.44							2.37
	22	2.37					2.27		2.39
	19	2.39				2.26			2.41
17**	**8****	**2.44****	**1.78****	**1.66****	**1.81****	**2.08****	**2.54****	**2.47****	**2.43****
ACa (range)		2.26-3.05	1.98-2.34	1.96 -2.43	1.97-2.37	2.04-2.67	2.21-2.58	2.19 -2.44	2.32-3.05
ACa (median)		2.45	2.29	2.13	2.17	2.29	2.32	2.26	2.49

Change of ACa (range)	0	(-0.75) - (+0.05)	(-0.47)-(0.12)	(-0.93)– (+0.11)	(-0.58)-(+0.12)	(-0.30) – (+0.11)	(-0.41) –(-0.05)	(-0.40)-(+0.83)
Change of ACa (median)	0	-0.51	-0.38	-0.34	-0.16	-0.14	-0.07	+0.02
№ of results per time window	25	6	4	12	9	8	3	13

** Patient received more than one dose of denosumab, baseline results listed in chronological order*, ********Patients No 7 and No 17 excluded from the statistics*

Table 2. Change in iPh, ALP, Albumin and eGRF following denosumab

Results		**Baseline**	**Time window following the denosumab (in days)**						
Analyte			**3-14**	**15-30**	**30-60**	**60-90**	**90-120**	**120-150**	**150-210**
IPh (mmol/L)	range	0.86-1.94	0.85-1.36	0.62-1.50	0.62-1.33	1.07-1.45	0.76-1.34	0.88-1.26	0.90-1.65
RR(0.80-1.40)	median	1.28	0.93	1	1.08	1.23	1.17	1.09	1.30
Change in iPh to baseline (mmol/L)	range		(-0.60)-(+0.04)	(-1.50) –(+ 0.27)	(-1.03)-(+0.31)	(-0.27)-(+0.22)	(-0.32)-(+0.10)	(-0.57)-(+0.29)	(-0.38)-(+0.96)
	median		-0.36	-0.34	-0.26	-0.20	+0.02	+0.28	+0.14
ALP(U/L)	range	26-336	56-130	57-196	48-198	50-101	27-150	51-129	30-145
RR(30-130)	median	81	93	65	79	69	59	100	61
Change in ALP to	range		(-2)-(-15)	(-1)-(-140)	(-131)-(+7)	(-263)-(+5)	(-124)-(+4)	(-264) - 0	(-198)- (+4)
baseline (U/L)	median		-13	-24	-10	-27	-9	-64	-14
Albumin(mmol/L)	range	34-45	32-44	41-44	25-44	36-43		25-44	34-45
RR(35-50)	median	38	42	42	39	41	40	41	37
Change in Albumin	range		(-3)-(+3)	(-4)-(+5)	(-10)-(+2)	(-5)-(+2)	(-3)-(+3)	(-10)-(+3)	(-7)-(+7)
(mmol/L) to baseline	median		+1	+2	2	0	1	+3	-2
eGFR	range	13-29	19-27	14-20	16-29	14-27	16-24	n/a	13-28
(mL/min/1.73m$^{2)}$	median	19	23	17	20	19	18	n/a	19
Change in eGFR to	range		(+2)-(+3)	(-1)-(+2)	(-14)-(+4)	(-2)-(+4)	(-5)-(+2)	n/a	(-3)-(+8)
baseline	median		3	0	1	1	-2	n/a	-3
Number of results per time window		25	6	4	12	9	8	3	13

In another study [6] *Block et al* investigated the effect of a single 60 mg dose of denosumab in patients with various degrees of renal impairment. The study included 9 patients with CKD 4 and 8 with CKD 5. ACa was measured on days (-1(baseline)), 2, 3, 6, 8, 11, 15, 22, 29, 43, 57, 85, and 113 post denosumab. Two subjects with CKD4 each experienced an adverse event of hypocalcaemia that was classified as serious due to hospital treatment; both were considered related to denosumab. One subject was symptomatic (perioral numbness with numbness and tingling of both feet) and the other subject was asymptomatic. Both subjects had iPTH above the target advised by KDIGO guidelines (iPTH should be within ref range in CKD 4). As a result of these the study protocol was amended, requirements for daily supplementation of calcium (up to 1000 mg) and vitamin D (up to 800 IU) were introduced and the enrolment criteria were tightened. Subjects with CKD 4 and 1,25-dihydroxyvitamin D <30 pg/mL, CKD4 and iPTH) >11.7 pmol/L (110 ng/L), or CKD5 and iPTH > 31.8 pmol/L (300 ng/L) we excluded from the study. After the study protocol was amended only two subjects (both kidney failure) had nadir concentrations (at day 8) <1.9 mmol/L, but both were non adherent to calcium supplementation and had prior histories of intermittent hypocalcaemia. The average nadir of hypocalcaemia in this study was found to be on day 8.[6]

Similarly to Block et al. study [6] the current study did not find any clinically significant hypocalcaemia in the appropriately supplemented patients.

There have also been several case reports on the issue on patients with CKD 4 and 5.[7-11] *Martín-Baez et al* reported a severe symptomatic hypocalcaemia with ACa 1.30 mmol/L on a 46 year old female with CKD 5 who was noncompliant with her supplementation.[6]

Talreja reported a severe symptomatic hypocalcaemia with ACa 1.68 mmol/L on a 68 year old female with CKD4.[8] However in this case it is not clear whether the patient was normocalcaemic when she received denosumab as the baseline ACa results were taken 4 months before administration and in the advanced stages of CKD ACa results often show significant fluctuations. No information was provided whether the patient was on any calcium or vitamin D supplementation and at baseline iPTH was not measured.

Toregrossa reported asymptomatic hypocalcaemia of 1.91 mmol/L at 6 months post dose in a renal transplant patient with CKD 4 treated with colecacliferol but not with calcium or calcitriol analogues.[9] However, iPTH of 45.1 pmol/L (not meeting KDIGO guidelines) suggests that the patient was under supplemented.

Mccormic et al. reported a case of 61 year old female HD patient who developed severe (1.34 mmol/L) hypocalcaemia, fatigue and malaise on day 30 , following injection of 60 mg denosumab [10]. The patient's supplements included 2.4 g elemental calcium a day but not any vitamin D supplements and 25(OH) vitamin D levels were not measured prior to denosumab. The pretreatment ACa result on the day of the injection was 2.22 mmol/L (unfortunately the reference range was not supplied) and was taken immediately prior to denosumab.

The same paper [10] also reported a case of 76 old female HD patient with normal pretreatment ACa and PTH of 45 pmol/L (no reference range provided but probably within KDIGO targets) who developed asymptomatic hypocalcaemia of 1.75 mmol/L following 60 mg of denosumab [10]. There was no data on the 25(OH) vitamin D levels or whether the patient was on any calcium and vitamin D supplementations.

Agarval et al reported a case of severe, symptomatic hypocalcaemia after denosumab in a 58-year-old Caucasian female with CKD 5 on peritoneal dialysis .[11] Baseline ACa, 25 OH vit D and iPTH results were within acceptable limits(KDIGO guidelines) and the patient was supplemented with colecalciferol and doxercalciferol (analogue of calcitriol) but not with oral calcium. The patient was previously on calcium supplements but they were discontinued because the patient had developed transient hypercalcaemia. 500 mg Calcium carbonate (equal to 200 mg elemental calcium) over-the-counter once daily was advised on the day of the injection. Current guidelines (HIH Medline plus, Winter 2011 Issue: Volume 5 Number 4 Page 12) advise at least 1200 mg elemental calcium for the age group).Unfortunately the authors did not provide any information on the dietary calcium intake or compliance. Hypothetically the patient may have been inadequately supplemented with calcium, although the clinical practice shows that unless calcium intake is extremely poor in most cases this problem can be overcome by increasing the dose of calcitriol (or its analogues).

There have been also some other reports of denosumab induced hypocalcaemia [10,15] but they relate to the cancer dose of the medication (120mg s.c.) and are not subject of the current study.

In summary, significant hypocalcaemia was seen in CKD 4 patients treated with denosumab when they did not receive calcium or vitamin D supplementation or were incompliant with it .[5] Due to its potent anti resorptive mechanism of action denosumab is the most likely cause of the hypocalcaemia . However , clinically significant hypocalcaemia has not been reported following denosumab in CKD4 when the patients regularly received calcium and vitamin D supplementation [5]. On the contrary, massive reduction in serum calcium has been reported in an unsuplemented, vitamin D deficient patient with CKD 4 and immobilisation hypercalcaemia (ACa 3.02 mmol/L) after denosumab [16].

Due to the scarcity of available data it is more difficult to assess the effect of denosumab in the CKD 5 subgroup (including the haemodialysis population). However so far clinically significant hypocalcaemia has not been reported when the patients received both calcium and calcitriol analogues supplementation and were compliant with their medications. In the first case reported by *McCormick et al* [10] the patient received only calcium supplementation but not any calcitriol analogues. This is very unusual for HD patients as the synthesis of 1-alpha hydroxylase in their kidneys is severely impaired and they are unable to convert the 25 OH vit D into calcitriol, which is the most active of the vitamin D metabolites. If these patients are not supplemented they rely exclusively on bone resorption to maintain their plasma calcium levels . Suppressing the osteoclasts by a potent anti resorptive agent would result in inability of bone calcium pool to participate in calcium homeostasis , therefore for these patients vitamin D supplementation is vital (especially in the form of calcitriol or its analogues).

Agarval et al 's report on hypocalcaemia after denosumab on a patient on peritoneal dialysis[11] deserves a special attention as despite missing some important data it may be the first case to describe clinically significant hypocalcaemia in an appropriately supplemented patient(although only with calcitriol analogues but not with calcium).

It appears that in the vast majority of the reports [5-11] published so far there was an easily identifiable cause of the hypocalcaemia and that supplementation with both calcium and calcitriol (or its analogues) is vital for these patients [5]. In CKD 4 and 5 bone resorption plays a major part in calcium homeostasis and when suppress it clinicians have to make sure that there is an adequate alternative way of supplying calcium.

It is difficult to define the exact amount of supplementation but achieving 25 OH vit D > 75 nmol/L and iPTH within KDIGO recommendations may be the minimum standard. In addition to that (especially in CKD5) aiming for pretreatment ACa levels in the upper half of reference range , increasing of the usual dose of calcium or vitamin D supplementation in the first 2-3 weeks or reduction of denosumab dose might be considered. Other important measures include taking baseline ACa levels strictly on the day of the injection, regular post dose monitoring and avoiding prescribing denosumab to patients who are unlikely to be compliant with the supplementation.

All these measures would require administering denosumab at a centre with significant expertise in osteoporosis rather than at the GP surgeries. These centres are also much more likely to have the expertise to identify the patients who are likely to have adynamic bone disease and hence be not suitable for antiresorptive therapy.

4. CONCLUSION

In appropriately supplemented patients there is no evidence that 60 mg denosumab can cause clinically significant hypocalcaemia in the CKD 4 subgroup and little evidence that that can happen in CKD 5 subgroup. However in CKD 5 subgroup the number of the reported cases so far is extremely small. More research is warranted especially in the CKD 5 subgroup. In the meantime more cautious approach with risk/benefit analysis on each individual patient rather than a blanket ban on denosumab in these subgroups appears more appropriate.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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