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Evaluation of estimated glomerular function (eGFR) versus creatinine clearance (CrCl) to predict acute kidney injury when using zoledronate for the treatment of osteoporosis

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Summary

Zoledronate could be contributing to the development of acute kidney injury in a small number of patients. Since estimated glomerular function (eGFR) is simpler to obtain and at least as good a predictor as creatinine clearance (CrCl), it should be used in everyday practice.

Abstract

Purpose:

Zoledronate is widely used for the treatment of osteoporosis. A potential side effect is acute kidney injury (AKI). Advice from the UK Medicines and Healthcare products Regulatory Agency (MHRA) in 2019 stated that CrCl and not eGFR should be used and that treatment should not be given if CrCl <35 ml/min. The objective of this study was to compare our current method of assessing renal function (eGFR) with the method proposed by the MHRA (CrCl) for predicting AKI after zoledronate infusions.

Methods:

The evaluation was performed at the Metabolic Bone Centre in Sheffield Teaching Hospitals, UK. Data on all the patients who had zoledronate from 1/09/2015 to 1/10/2020 were included.

Results:

Data on 4405 patients were retrieved (total number of infusions 7660). Creatinine in the 14 days post-infusion was available for a total of 969 infusions and AKI was observed within 14 days following 45 infusions (4.6%). One patient died due to pneumonia. One patient needed continued haemodialysis. Severe AKI (threefold in creatinine and/or eGFR<15 ml/min/173m2) was observed within 1 year following 24 infusions.

If the MHRA recommendations had been followed, 996 infusions with baseline CrCl<35 ml/min would not have been given. Of these, follow up data on serum creatinine within 14 days was available for 142 infusions; showing AKI in only four (2.8%). Logistic regression showed that both CrCl and eGFR were significant factors in predicting AKI within 14 days, but that the current recommended cut-off of CrCl 35 ml/min had poor sensitivity.

Conclusions:

Since eGFR is at least as good a predictor of AKI as CrCl, and permits the treatment of more patients at high fracture risk, we recommend that eGFR is used to determine renal function for zoledronate treatment. We suggest that the infusion is given over 30 minutes in patients with eGFR <50 ml/min/1.73m2.

Keywords

Zoledronic acid; zoledronate; kidney; acute kidney injury; bisphosphonate; osteoporosis

Declarations

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NP no conflicts

LTU no conflicts

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Availability of data and material

Not applicable

Author's contributions

The authors confirm that the manuscript is original and has not been submitted elsewhere. Each author acknowledges that he/she has contributed in a substantial way to the work described in the manuscript and its preparation.

Ethics approval/ Consent to participate/ Consent for publication

Not applicable (service evaluation)

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Introduction

Zoledronate is a medication widely used for the treatment of osteoporosis. Treatment leads to improvements in bone mineral density and reductions in fractures. It is given in annual infusions. Its mechanism of action is through the inhibition of farnesyl pyrophosphate synthase (FPS), an enzyme in the mevalonate pathway for cholesterol biosynthesis. This pathway is required for post-translational lipid modification

(prenylation) and anchoring of small GTPases in cell membranes, a process which is critical for a variety of cellular processes. When zoledronate is given, the resulting decrease in prenylated protein levels induces osteoclast apoptosis (Perazella & Markowitz, 2008).

Zoledronate is excreted unchanged; impaired renal function can reduce its excretion and can lead to excessive serum levels and toxicity. The mechanism behind this is thought to be similar to the action observed in osteoclasts (Perazella & Markowitz, 2008).

In everyday practice, the use of this medication is restricted in patients with reduced kidney function. The British National Formulary (BNF) recommends using zoledronate only in patients with an estimated glomerular filtration rate (eGFR) >35ml/min/1.73m^2 (https://bnf.nice.org.uk/drug/zoledronic-acid.html) while the product licensing states that zoledronate treatment is contra-indicated in patients with a CrCl less than 35ml/min calculated using the Cockcroft and Gault formula (CG) (EMC).

Recent advice from the Medicines and Healthcare products Regulatory Agency (MHRA) states that for most drugs and most situations, eGFR is an acceptable estimate of renal function. However, it can overestimate renal function compared with CrCl. This overestimation can result in patients receiving higher than recommended doses of their medicine. The advice concludes that for patients over 75 years and those at extremes of body weight, CrCl should be used to guide and make decisions about treatment and that patients should not receive zoledronate if their CrCl is below 35 ml/min (MHRA, 2019).

Prior to publication of the MHRA advice, day-to-day practice within the Metabolic Bone Centre (MBC) in Sheffield Teaching Hospitals National Health Service Foundation Trust (STH NHS FT) used the eGFR to guide treatment with IV zoledronate as per the BNF, offering treatment to patients with an eGFR greater than 35ml/min. In borderline eGFR levels (close to 35 ml/min/1.73m^2), the practice was to extend the time of infusion from 15 minutes to 30 minutes.

Our objective was to compare the established method of assessing renal function (eGFR) with the method proposed by the MHRA (CrCl) for predicting AKI after zoledronate infusions. Our hypothesis is that eGFR is equally useful as CrCl in predicting AKI after zoledronate.

Materials and methods

We undertook a retrospective review of zoledronate treatment administered at the Metabolic Bone Centre (MBC) in Sheffield Teaching Hospitals NHS FT. It was registered as a service evaluation project and received approval from the Clinical Effectiveness Unit (CEU) in November 2020, reference number 10198.

Data on all the patients who had zoledronate infusions from 1/09/2015 to 1/10/2020 at the Centre were retrieved. For each patient, date of birth, postcode and gender were included. In order to maximise access to relevant clinical information, we only included patients who were living in Sheffield postcodes. Patients receiving zoledronate infusions at the MBC are documented in a departmental database. Information on the date of infusion and the number of infusion (e.g. whether it was the first, second etc) during this period were retrieved. We requested data on all the available creatinine values on the intranet from the 1st January 2015. We defined "baseline creatinine" as the value that preceded each infusion most closely and within a period of two months. We defined "follow up creatinine" as the first measurement that was performed after the infusion. Creatinine was measured using a Roche/Hitachi Cobas c8000 e702 analyser (Roche Diagnostics GmbH, Mannheim, Germany). Height and weight for each patient were retrieved from the bone mineral density scans closest to each infusion. After the data was received, we assigned a study ID to each patient to ensure anonymisation.

For the calculation of CrCl, an online calculator was used (https://www.mdcalc.com/creatinine-clearance-cockcroft-gault-equation). This calculates CrCl using the Cockcroft-Gault method as follows:

$$CrCl\left(\frac{mL}{min}\right) = (140 - age, years)\ x \frac{weight, kg}{0.814 \times SCr, \mu mol/L}\ x\ 0.85\ (if\ female)$$

The result is adjusted based on the height and the weight of the patient, after calculating their body mass index (BMI). For underweight patients (BMI<18.5 kg/m^2),

the actual body weight is used. For normal BMI (18.5-24.9 kg/m^2), the ideal body weight (IBW) is used, which is calculated as follows:

Ideal body weight, kg = Constant + 0.91 (Height, cm - 152.4)

Where constant = 50 for men; 45.5 for women

For overweight and obese patients (BMI ≥25 kg/m^2), an adjustment factor of 40% is applied to the patient's excess weight over their ideal weight, in order to calculate the adjusted ideal body weight (ABW) as follows:

ABW, kg = IBW, kg + 0.4 × (actual body weight, kg – IBW, kg).

Estimated glomerular filtration rate (eGFR) was calculated at all time points using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (KDIGO, 2012).

To identify patients whose renal function could have been negatively affected by their treatment, we looked for evidence of acute kidney injury (AKI) within 14 days of the infusion. AKI was defined as

AKI: Follow up creatinine/ baseline creatinine ≥ 1.5

We only evaluated the patients who had AKI within 14 days of the infusion, as we would expect any effect of zoledronate as a contributory factor to occur within this time-frame.

In order to identify patients who had severe AKI, the following criteria were followed: follow up eGFR after infusion (within 1 year) ≤15 ml/min/1.73m^2 (consistent with CKD stage 5/kidney failure) and/or follow up creatinine/baseline creatinine ratio ≥3 (within 1 year), which is considered as stage 3 according to the Risk, Injury, Failure; Loss and End-stage kidney disease (RIFLE) system (Kellum et al, 2013).

In order to check for agreement between two tests, the Passing and Bablok and Bland and Altman graphs were used. To identify whether either test is a good predictive marker for AKI, receiver operating characteristic (ROC) curves were used. Finally, we explored predictors of AKI in this cohort using stepwise logistic regression. Comparison between two groups in terms of continuous variables was done using the Student's t test. A result was considered statistically significant if the p value was below 0.05. The statistical analyses were performed in MedCalc Software (MedCalc, Ostend Belgium) and RStudio (RStudio, Boston MA, USA).

Results

Baseline characteristics

Data on 4405 patients were retrieved, with a total of 7660 infusions having complete data of creatinine before (within 2 months) and after the infusion (within 1 year). The baseline characteristics are shown in Table 1.

	Patients (n=4405)
Age in years, median (IQR)	75 (66 - 83)
Female, n (%)	3533 (80.2)
BMI, kg/m^2, mean (SD)	26.0 (5.3)

Table 1: Baseline characteristics of the population. BMI: body mass index

Tests used for estimating kidney function

We first checked whether there was good agreement between CrCl and eGFR. Overall, eGFR was higher than CrCl and a CrCl of 35 ml/min, was found to be equivalent to eGFR of 56 ml/min/1.73m^2 (Figure 1).

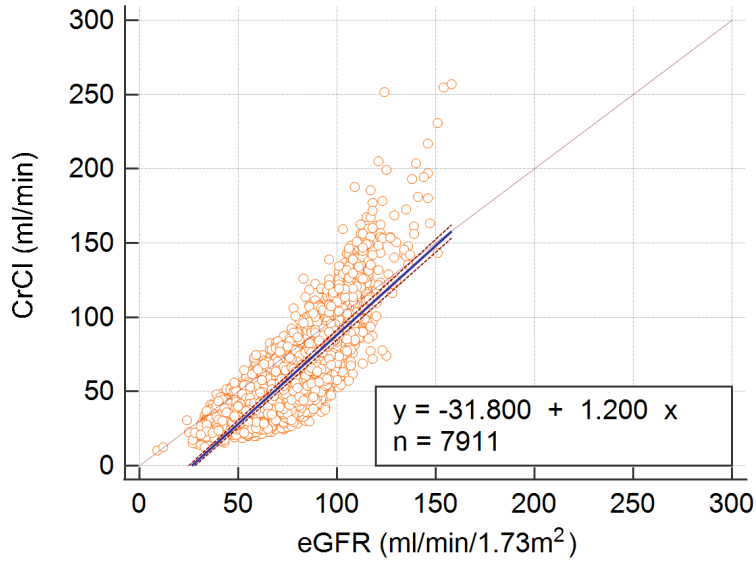

Figure 1: Passing and Bablok graph comparing creatinine clearance to eGFR

Determining whether pre-treatment CrCl or eGFR are good predictive markers for AKI, ROC curves were examined which showed an area under the curve of 0.608 (95% CI

0.573 to 0.642) and 0.627 (95% CI 0.593 to 0.660) respectively, suggesting that neither of these estimations of kidney function is reliable in predicting AKI (Figure 2). The optimal cut-off for CrCl was 49 ml/min, with a sensitivity of 66% and a specificity of 56%; for eGFR, this was 45 ml/min/1.73m^2 with a sensitivity of 32% and a specificity of 91%.

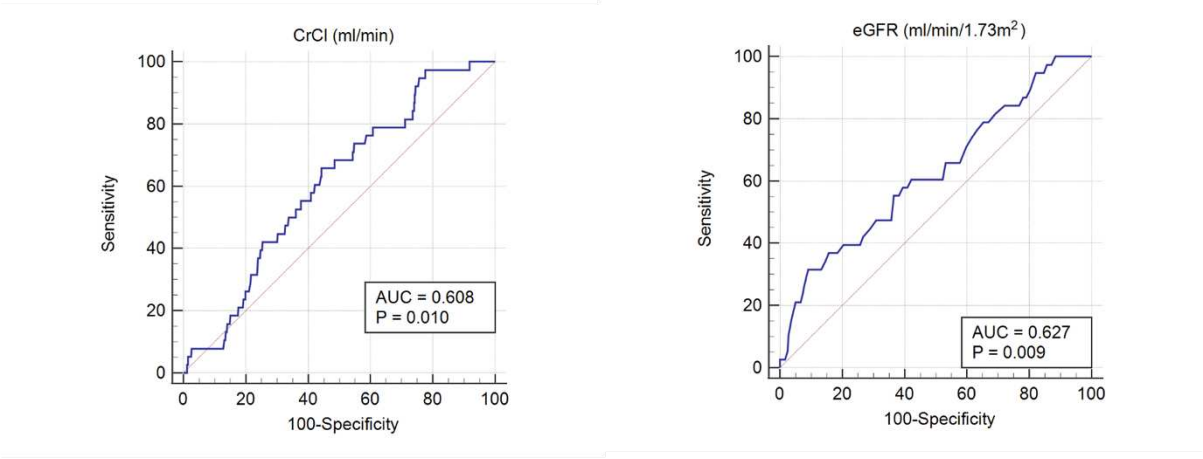

Figure 2: ROC curves evaluating CrCl (left) and eGFR (right) in predicting episodes of acute kidney injury.

Acute kidney injury events within 14 days of infusion

Serum creatinine in the 14 days post-infusion was available for a total of 969 infusions (out of a total of 7660). AKI was observed within 14 days following 45 infusions; two patients had more than one episode of AKI. This was characterised usually by a transient elevation in serum creatinine, in all cases but two as described below.

If the MHRA advice had been followed (calculating CrCl for patients aged ≥75years and/or extreme BMI <18 or >40 kg/m^2), 996 infusions with a baseline CrCl<35 ml/min would not have been given (out of a total of 7660). Out of them, follow up data on serum creatinine within 14 days was available for 142 infusions; only four infusions resulted in AKI.

In exceptional circumstances and after discussion with the renal physicians, six patients with eGFR lower than 30 ml/min/1.73m^2 were treated. Five of them were female (mean age 84 years) and their eGFR ranged from 20 to 24 ml/min/1.73m^2. None of them had an episode of AKI following treatment. One male patient on haemodialysis had three infusions.

When comparing patients who had AKI within 14 days with those who did not, there was no statistical difference in mean age (p=0.129), and BMI (p=0.067), but baseline CrCl was lower (46 vs 57 ml/min, p<0.001).

Logistic regression showed that CrCl was a significant factor in predicting AKI within 14 days, but not if the current recommended cut-off of 35 ml/min was used. If the cut-offs recommended by the ROC curves described above were used, both CrCl ≤49. ml/min and eGFR ≤45 ml/min/1.73m^2 were found to be significant predictors (Table 2).

Factors	Significant factors	Estimates	P value
Age, BMI, gender, CrCl	BMI CrCl	0.07 -0.03	0.023 0.008
Age, BMI, gender, eGFR	eGFR	-0.03	0.001
Age, BMI, gender, CrCl <35 ml/min (Y/N)	None	NA	NA
Age, BMI, gender, CrCl ≤49.1 ml/min (Y/N)	BMI CrCl ≤49.1 ml/min (Y/N)	0.06 -1.00	0.027 0.005
Age, BMI, gender, eGFR ≤45 ml/min/1.73m^2 (Y/N)	eGFR ≤45 ml/min/1.73m^2 (Y/N)	-1.49	<0.001

Table 2: Results of logistic regression with outcome of acute kidney injury within 14 days of infusion. BMI: body mass index, CrCl: creatinine clearance, eGFR: estimated glomerular rate, Y/N: yes or no (binomial factor)

Review of medical records in the patients with AKI events revealed a number of reasons for assessing renal function. Blood tests were performed by the patient's general practitioner (GP) on 17 occasions (38%, 7 patients had a hospital admission soon after), during an outpatient department appointment on 7 occasions (16%, 1 patient was admitted afterwards) and during in-hospital admission in 21 occasions (47%). Reasons for hospital admissions included: shortness of breath/ cough/ fever, n=6; altered mental status (confusion, drowsiness, lethargy), n=5; fall and/or syncope, n=5; other. One patient died during admission due to pneumonia (81y, baseline CrCl 50 ml/min). One patient needed continued haemodialysis after discharge (82y, admitted with complete heart block, baseline CrCl 36 ml/min).

Cases of severe kidney impairment within one year

We identified 24 cases of AKI which developed within a year following zoledronate treatment (0.3% amongst the 7660 infusions with data within 1 y). Amongst these: only 6 (25%) had CrCl < 35 ml/min before the infusion. Four patients amongst the ones identified as having severe AKI died within one year (14-287 days after the infusion), of which two had CrCl <35 ml/min at baseline. The causes of death included acute pancreatitis (n=2), COPD/heart failure (n=1) and hyponatraemia, chest infection (n=1). Four patients needed new courses of haemodialysis, none had baseline CrCl <35 ml/min. The other 15 patients discharged had baseline CrCl ranging from 24 to 96 ml/min. In the majority of patients, there was an underlying contributing factor for AKI (eg gastroenteritis, respiratory infection, cardiac problems, other medication toxicity etc) (Table 3) (Figure 3).

	Baseline eGFR	Number of infusion
Age (years)	Post-treatment eGFR (ml/min/1.73m^2)	Days after infusion
Discharge, no need of haemodialysis		
AKI<14 days		
87	34 13	1 10
84	66 16	3 7
79	68 14	1 8
83	69 8	1 13
76	91 17	6 9
AKI≥14 days		
77	35 8	5 17
88	36 15	5 62
82	37 11	2 206
76	42 15	1 21
85	48 4	1 44
71	62 7	1 22
41	79 14	1 35
	94	2

70	27	60
56	98 16	3 100
65	114 47	3 196
New haemodialysis		
AKI<14 days		
82	42 5	6 13
AKI≥14 days		
75	44 4	1 14
64	46 4	1 19
55	88 15	1 43
Death		
AKI≥14 days		
90	37 3	4 14
90	49 13	2 287
60	57 15	5 29
71	88 12	1 95

Table 3: Unique patients with severe kidney impairment defined as: eGFR≤15 ml/min/1.73m2 and/or follow up/baseline creatinine >3.0. Results within each category are shown by increasing baseline eGFR

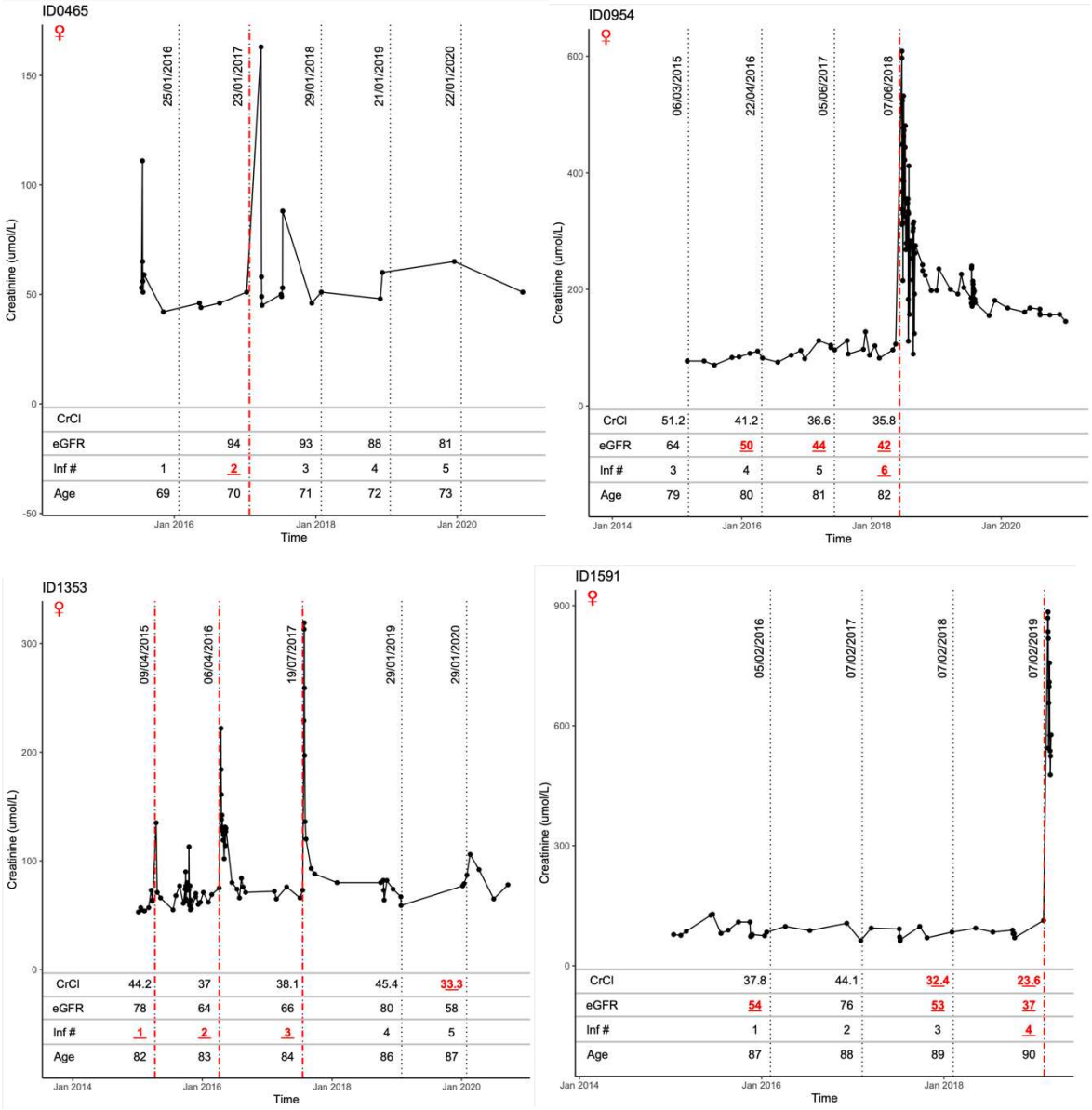

Figure 3: Examples of patients with severe kidney impairment defined by: eGFR≤15 ml/min/1.73m^2 and/or follow up/baseline creatinine >3.0. Vertical lines demonstrate infusions of zoledronate (number of infusion inf #) and red vertical lines demonstrate infusions that lead into AKI events. CrCl: creatinine clearance at baseline, values <35ml/min shown in red; eGFR: estimated glomerular rate, values <56 ml/min/1.73m^2 shown in red (identified by the Passing and Altman graph as equivalent to CrCl<35ml/min) . ID 0465: 60 days after the infusion, full recovery; ID0954: 13 days after the infusion, haemodialysis; ID 1353: all episodes within 14 days, full recovery; ID1591: 14 days after the infusion, death.

Discussion

This large retrospective evaluation suggests that zoledronate may have contributed to the development of AKI in a small proportion of patients treated for osteoporosis but neither pre-treatment eGFR nor CrCl were good predictors of AKI. The creatinine clearance cut-off of 35ml/min proposed by the MHRA did not predict patients who

subsequently developed AKI. It is worth noting that both eGFR and CrCl use creatinine-based estimation equations and thus, are subject to some physiological limitations. Our recommendation is to use eGFR as this is the recommended estimation of renal function (Levey & Stevens, 2010), it is already implemented in laboratory reports, our service evaluation has proven that it is safe to do so, and allows treatment of more patients at high risk of fracture.

Zoledronate is a very beneficial treatment for osteoporosis leading to improvement in bone mineral density and reduction of fracture risk. The current study does not provide direct evidence of harm as we did not have a placebo group. The Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) Pivotal Fracture Trial was a double-blind, placebo-controlled trial examining the effect of zoledronate 5 mg versus placebo once per year for 3 years in 7765 women with postmenopausal osteoporosis. This study showed a reduction of vertebral fractures by 70% and hip fractures by 41%. When evaluating the renal safety, researchers looked for an increase in creatinine concentration >0.5 mg/dl at 9-11 days after the infusion; this was observed more commonly in the zoledronate group [n=31 (1.3%) than placebo n=10 (0.4%); P=0.001]. The percentage of patients with increased Cr was greatest in those with baseline estimated CrCl between 30 and 34ml/min (10.6%) calculated using the Cockcroft–Gault method. In total, 85% of the patients returned to pre-infusion Cr levels within 30 days, while the rest returned to normal before their next infusion. The study reported that there was no significant difference in renal function between the two groups at the end the three-year period. The HORIZON study did not include patients with CrCl <30 ml/min (Black et al, 2007). Another study evaluating these results further, concluded that changes in renal function after annual infusions of zoledronate are very uncommon, mild, and transient and are not associated with any long-term detrimental effects in subjects with postmenopausal osteoporosis with CrCl >30 ml/min (Boonen et al, 2008). Not all parenteral bisphosphonates have been associated with renal damage, as shown in studies for ibandronate (Miller et al, 2013; Miller et al, 2011)

In the HORIZON-Recurrent Fracture Trial (RFT), annual infusions of zoledronate or placebo were given to 2127 men and women who had experienced a recent, low-

trauma hip fracture. The renal adverse events were similar across both groups (increase in creatinine within 4 weeks >0.5 mg/dL, 6.2% vs 5.6%) (Lyles et al, 2007). In the HORIZON-Glucocorticoid-Induced Osteoporosis (GIO) study, 833 patients with glucocorticoid-induced osteoporosis were randomised 1:1 to receive zoledronate (n=416) or risedronate (n=417). All patients had CrCl >30 ml/min. The number of patients with an increase of creatinine of >44 mmol/L (cut-off set by the researchers) was similar between the groups. Two patients from the zoledronate group and two from the risedronate group experienced AKI but the events were considered to be related to underlying diseases (Reid, 2009). Patients receiving zoledronate often have multi-morbidity, as shown in our cohort, and most of the AKI we found was primarily due to another cause than zoledronate. However, the risk of AKI needs to be taken in consideration.

The effect of zoledronate on renal safety was also assessed in a study which randomised osteopenic older women to either four infusions of zoledronate or normal saline every 18 months. This study showed there was no difference in renal adverse events between zoledronate and placebo (Reid et al, 2020).

Our data have shown episodes of AKI which had temporal relationship to zoledronate treatment in a small proportion of patients, similar to the frequency observed in the HORIZON trial. It is reasonable to assume that the bisphosphonate was a contributing factor in some of these cases. However, there was no control group, and the incidence of AKI in the Horizon trial was similar in the zoledronate and placebo group, so we cannot be sure how many cases would have occurred in our patients without zoledronate treatment. The majority of patients who had AKI did not have a low baseline CrCl as defined by the MHRA. The Cockcroft and Gault formula for CrCl (CG) was developed several years ago (1973). In order to derive this equation, date from only 249 male patients aged 18-92 were used (Cockcroft & Gault, 1976). It is important to consider this in relation to zoledronate, as it is given predominantly to women. One other limitation is that non-standardized creatinine values were used for its calculation. Therefore, this formula is no longer recommended for use. More accurate estimation using the CKD-EPI equation should be used in everyday practice (Levey & Stevens, 2010). Based on ROC analysis and logistic regression, an eGFR of 45 ml/min/1.73m^2 could be used in clinical practice to identify individuals who may be at increased risk

of AKI and in whom additional measures may be advisable to minimise this risk. For example, treatment may be administered more slowly (30 minutes rather than the recommended 15 minutes). We would estimate that doubling the infusion time would half the maximum concentration of zoledronate in the serum. There have been studies that have suggested that smaller doses could also be used, but, currently, the licenced dose is 5mg (Grey et al, 2017)

It is important to consider the anticipated benefit to bone health in deciding whether to treat patients with impaired kidney function and whether the risk outweighs the benefit. A recent study suggested that there is a gradual decrease in the absolute gains in bone mineral density in oral bisphosphonate users with decreasing renal function though there was no significant interaction. The limitation of this study was the small numbers of patients with more advanced stages of CKD (Abrahamsen et al, 2020). More data are needed before drawing any conclusions. One also needs to consider the mortality after fractures; one third of patients die within a year after a hip fracture (Jiang et al, 2005), so it is important to be treat patients who are at risk of fracture..

The strengths of our evaluation were the use of real-life data and the large number of participants and infusions. Limitations include the retrospective design, the fact that heights and weights were retrieved from DXA scans performed in some cases several months away from the infusion, and inability to access clinical data from GP records in a proportion of cases. Moreover, only a small proportion of patients had follow up bloods at two weeks. The tests might have been taken because the patients were unwell. Thus, the reported percentage of AKI could be an overestimate.

Our evaluation suggested that zoledronate could be contributing to the development of AKI in some patients but neither eGFR nor CrCl are good predictive markers. The physician needs to consider that both eGFR and CrCl are estimations and thus, should individualise the decision of treating a patient with zoledronate and not base the decision purely on a calculated cut-off. Good hydration should be advised to all patients receiving zoledronate, especially if they are on diuretics, Non-steroidal anti-inflammatory drugs (NSAIDs) and/or have impaired kidney function. It is good practice to reinforce the verbal advice with written information the patient can refer to at home. We suggest that because eGFR <45 ml/min/1.73m^2 was predictive of AKI, the infusion

is given over 30 minutes in patients with eGFR <50 ml/min/1.73m^2. Since eGFR is at least as good a predictor of AKI as CrCl, and permits the treatment of more patients at high fracture risk, we recommend that eGFR is used to determine renal function for zoledronate treatment for osteoporosis.

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