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Fracture Risk Reduction by Bisphosphonates in Mastocytosis?

Merel C. Onnes, MD^a, Jasper J. van Doormaal, MD, PhD^a, Eveline van der Veer, PhD^b, Joris B. Versluijs, MD^a, Suzanne Arends, PhD^c, and Hanneke N.G. Oude Elberink, MD, PhD^a Groningen, the Netherlands

What is already known about this topic? Patients with indolent systemic mastocytosis are at high risk of fragility fractures.

What does this article add to our knowledge? The risk of fragility fractures remains high in spite of bisphosphonate treatment.

How does this study impact current management guidelines? These findings highlight the need for further interventional studies on the matter.

BACKGROUND: Fragility fractures (FFxs) and osteoporosis are frequent manifestations of indolent systemic mastocytosis (ISM). So far, the effect of antiosteoporotic therapy on FFxs has scarcely been investigated.

OBJECTIVE: This study evaluates the long-term effect of bisphosphonate treatment on FFxs, bone mineral density (BMD), and bone resorption in patients with ISM in daily clinical practice.

METHODS: Patients with ISM who received bisphosphonates because of osteoporosis and/or FFxs were retrospectively analyzed ($n = 58$). Fractures were recorded by vertebral fracture assessment, X-rays of the thoracolumbar spine, medical records, and a questionnaire. Five-year analysis ($n = 30$) was made by comparing observed 5-year FFx risk with MastFx-predicted FFx risk for patients with ISM not treated with antiosteoporotic drugs and analyzing 5-year change in BMD and serum collagen C telopeptide (sCTX) Z-scores.

RESULTS: During the median follow-up of 7.3 years, 14 of 58 patients suffered 40 FFxs. Five- and 10-year FFx-free survival were 81.9% (standard error [SE], 5.5%) and 67.0% (SE, 7.7%),

respectively. FFx risk was significantly higher in patients with previous vertebral FFxs ($P = .004$), lower femoral BMD at baseline ($P = .042$), and history of anaphylaxis ($P = .028$). No 5-year FFx risk reduction could be proven, possibly due to the small sample size. The lumbar BMD Z-score significantly increased from median (interquartile range [IQR]) -2.20 (-2.80 to -1.50) to -1.50 (-2.30 to -0.60) ($P < .001$, $n = 27$). The sCTX Z-score decreased from median 0.71 (IQR, -0.59 to 2.39) to -0.95 (-1.30 to -0.16) ($P = .008$, $n = 15$).

CONCLUSION: Bisphosphonates significantly increase BMD and decrease sCTX in patients with ISM. However, FFxs still frequently occur. Especially patients with previous FFxs remain at high risk of new FFxs. © 2020 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;8:3557-64)

Key words: Indolent systemic mastocytosis; ISM; Mastocytosis; Fragility fractures; Osteoporosis; Bisphosphonates; Bone mineral density; Bone turnover; Treatment outcome; Tryptase

Indolent systemic mastocytosis (ISM) is a mast cell proliferation disorder characterized by proliferation, accumulation, and degranulation of pathological mast cells in extracutaneous tissue(s), frequently bone marrow.¹⁻³ Fragility fractures (FFxs), or low-energy trauma fractures, are frequently observed in patients with ISM inducing a high burden of disease in a relatively young and frequently male patient population.^{4,5} The reported lifetime prevalence of FFxs is 41% (mean age 51 years).⁶ Furthermore, the observed prevalence of osteoporosis varies from 18% to 31%.^{3-5,7,8}

In ISM, bone metabolism is disturbed by local mast cell infiltration and local mast cell mediator release. Mast cell products such as histamine, tryptase, heparin, IL-6, and RANKL interfere with bone metabolism through various not fully elucidated pathways. In patients with ISM with bone manifestations, this results in a relative overactivity of osteoclasts.^{5,9-12} Bisphosphonates are the first-line drugs for treating osteoporosis. They inhibit osteoclast activity, inducing an antiresorptive effect. The consecutive increase in bone mineral density (BMD)

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Abbreviations used

BMD- Bone mineral density

FFxs- Fragility fractures

HE fractures- High energetic trauma fractures

ISM- Indolent systemic mastocytosis

IQR- Interquartile range

MH- Methylhistamine

MIMA- Methylimidazole acetic acid

MPR- Medication possession rate

sCTx- C-terminal telopeptide in serum

SD- Standard deviation

SE- Standard error

UMCG- University Medical Center Groningen

VFA- Vertebral fracture assessment

results in prevention of FFxs. This FFx risk reduction has been extensively demonstrated in postmenopausal osteoporosis.^{13,14} However, given the differences in pathophysiology in ISM, it is questionable whether bisphosphonates would have sufficient FFx reducing capacity in ISM.

In ISM, bisphosphonates are advised in the management of osteoporosis as they increase BMD in this population.¹⁵ Several small-scale studies on bisphosphonate use in ISM have been conducted so far.^{7,16-20} The 2 largest studies respectively assessed the effect of zoledronic acid in 25 patients with 1-year follow-up,¹⁶ and of several oral bisphosphonates in only 9 patients with a median follow-up of 65 months (range, 26-84 months).⁷ Both studies showed an increase in BMD. No FFxs were observed during follow-up. However, methods of fracture detection were not described. Also, the duration of follow-up was relatively short for this assessment.

In our clinic, we observed new FFxs in spite of bisphosphonate treatment. Therefore, we questioned the efficacy of this treatment. This current study adds to the existing literature by analyzing the long-term effectiveness of bisphosphonate treatment in 58 patients with ISM, focusing primarily on FFxs, and secondarily on change in BMD and the bone resorption marker serum type 1 collagen C telopeptide (sCTx).

MATERIALS AND METHODS

Study design

This study of the Dutch National Center for expertise on Mastocytosis of the University Medical Center Groningen (UMCG), the Netherlands, retrospectively analyzed the long-term effectiveness of bisphosphonate treatment in patients with ISM on number and risk of FFxs, and change in BMD and bone resorption in daily clinical practice.

The included patients received their first dose of bisphosphonates before November 2013. Follow-up data were gathered until November 2018. The Medical Ethical Review Board of the UMCG declared that the study was performed in accordance with regulations of the review board for publication of subjects' data.

Study population

The enrolled patients had been diagnosed with ISM according to the WHO criteria.²¹ Patients received bisphosphonate treatment because of a history of FFxs and/or osteoporosis, defined according to the WHO criteria as a BMD *T*-score of the lumbar spine or femur of ≤ -2.5 .²² In compliance with guidelines, all patients were supplemented with calcium and vitamin D.²³⁻²⁵

FIGURE 1. Flowchart of inclusion and exclusion. Patients who did not give informed consent, patients with a short duration of follow-up, and patients who used bone metabolism or mastocytosis interfering therapies were excluded. In total, 58 patients were included. Of them, 30 had both baseline and 5-year (± 1 year) data of vertebral fracture assessment and/or X-rays of the thoracolumbar spine. These patients were used for the 5-year secondary outcome analyses. *ISM*, Indolent systemic mastocytosis; *VFA*, vertebral fracture assessment.

Of a total of 76 patients with ISM treated with bisphosphonates, 58 were included. Excluded patients did not give informed consent ($n = 6$), started treatment after 2013 ($n = 8$), or received therapies interfering with bone metabolism or mastocytosis (ie, other antiosteoporotics, mast cell eradication therapy, extensive hormonal treatment, $n = 4$). A flowchart of inclusion and exclusion is given in [Figure 1](#).

Outcome measurements

Primary outcomes were the percentage of patients with FFxs, the total number of FFxs, and the 5- and 10-year FFx-free survival after the start of bisphosphonate treatment for the total patient group ($n = 58$). Fracture history data were collected from a patient questionnaire and medical records. Distinction was made between high energetic trauma (HE) and FFxs resulting from the mechanical impact that would not ordinarily result in fractures.²⁶

Vertebral fractures were identified on vertebral fracture assessment (VFA) or conventional X-rays from lateral radiographs of the thoracolumbar spine, using 20% height reduction as the cutoff value.²⁷ An independent nuclear medicine physician reassessed the

TABLE I. Baseline characteristics of the total included patient group (n = 58), as well as the comparison of the patients with and without complete baseline and 5-year VFA/X-ray measurements

Variable	Total patient group (n = 58)			Patients with baseline and 5-y VFA/X-ray data		
	n		n	Complete dataset (n = 30)	Incomplete dataset (n = 28)	P value (n = 30 vs n = 28)
Age at diagnosis ISM	58	52.7 (10.1)	30 28	50.7 (9.5)	54.8 (10.4)	.127
Age at the start of treatment	58	55.2 (10.3)	30 28	54.0 (7.9)	56.6 (12.4)	.351
Male gender	58	27 (46.6%)	30 28	14 (46.7%)	13 (46.4%)	.986
Postmenopausal status women	31	29 (93.5%)	16 15	15 (93.8%)	14 (93.3%)	≥.999
Urticaria pigmentosa	58	36 (62.1%)	30 28	19 (63.3%)	17 (60.7%)	.837
History of anaphylaxis	58	25 (43.1%)	30 28	15 (50%)	10 (35.7%)	.301
Body mass index (kg/m ²)	41	25.3 (4.0)	26 15	24.8 (3.7)	26.1 (4.4)	.320
Fracture history						
FFx, vertebral	58	15 (25.9%)	30 28	9 (30%)	6 (21.4%)	.456
FFx, other	58	4 (6.9%)	30 28	2 (6.7%)	2 (7.1%)	≥.999
HE fractures	58	28 (48.3%)	30 28	12 (40%)	16 (57.1%)	.196
Serum tryptase (μg/L)	51	37.1 (22.0 to 77.0)	29 22	32.3 (20.4 to 76.7)	38.5 (25.2 to 94.2)	.746
Urinary MH (μmol/mol creatinine)	54	323.0 (214.8 to 509.3)	30 24	324.5 (213.8 to 630.5)	313.5 (210.3 to 447.0)	.525
Urinary MIMA (mmol/mol creatinine)	53	4.1 (2.6 to 6.4)	29 24	4.1 (2.7 to 6.2)	4.1 (2.5 to 6.4)	.789
Total IgE (kU/L)	50	19.4 (12.40 to 45.68)	28 22	18.95 (12.05 to 51.53)	21.15 (12.40 to 42.45)	.969
Bone mineral density						
Lumbar, T-score	36	−2.65 (−3.00 to −2.13)	27 9	−2.70 (−3.40 to −2.40)	−2.10 (−2.75 to −0.95)	.036
Lumbar, Z-score	36	−1.70 (−2.50 to −1.20)	27 9	−2.20 (−2.80 to −1.50)	−1.20 (−1.55 to 0.15)	.009
Femoral, T-score	37	−1.30 (−1.90 to −0.60)	27 10	−1.40 (−2.00 to −0.60)	−1.00 (−1.65 to −0.65)	.468
Femoral, Z-score	37	−0.70 (−1.15 to −0.05)	28 9	−0.90 (−1.20 to −0.10)	−0.30 (−0.95 to 0.75)	.116
sCTX Z-score	32	0.54 (−0.40 to 2.20)	25 7	0.85 (−0.10 to 2.69)	0.01 (−1.33 to 0.26)	.030
Use of H1 antagonists	55	21 (38.2%)	30 25	11 (36.7%)	10 (40%)	.800
Use of H2 antagonists	54	19 (35.2%)	30 24	9 (30%)	10 (41.7%)	.372
Alcohol	52		27 25			.674
Intolerance		7 (13.5%)		4 (14.8%)	3 (12%)	
Tolerance		41 (78.9%)		22 (81.5%)	19 (76%)	
Abuse		4 (7.7%)		1 (3.7%)	3 (12%)	
Smoking status	55		30 25			.358
Current		22 (40%)		14 (46.7%)	8 (30.7%)	
Quit (≥1 y)		8 (14.5%)		5 (16.7%)	3 (11.5%)	
Never		25 (45.5%)		11 (36.7%)	14 (53.8%)	

FFx, Fragility fractures; HE, high energetic trauma; ISM, indolent systemic mastocytosis; MH, methylhistamine; MIMA, methylimidazole acetic acid; sCTX, serum collagen C telopeptide; VFA, vertebral fracture assessment.

Data are given as numbers (% of group) and median (IQR). The number of patients in whom parameters were available is given, as some parameters had not routinely been performed. Bold values indicate statistical significance ($P < .05$).

images. Moment of fracturing was defined as the date of VFA or X-ray on which the fracture was first objectified. Characteristics of patients who did and did not develop FFxs during follow-up were compared with identify risk factors for fractures during therapy.

For secondary outcome assessment, patients with both baseline and 5-year (± 1 year) VFA or X-rays of the thoracolumbar spine were included (n = 30 of 58). The duration of 5 years was chosen as it is in line with our aim for long-term assessment of treatment and as this duration is conventional in postmenopausal osteoporosis guidelines.²³⁻²⁵ Secondary outcome assessment concerns a 5-year change in BMD and sCTX.

We also compared the observed 5-year FFx risk under bisphosphonate treatment with the MastFx score⁶ predicted 5-year FFx risk without antiosteoporotic treatment. The MastFx score is a fracture risk scoring tool developed in our center for patients with ISM not treated with antiosteoporotic drugs. Male sex, sCTX Z-score $\geq +1.0$, femoral BMD T-score ≤ -1.0 , absence of urticaria

pigmentosa, and presence of alcohol intake were identified as independent risk factors. Predicted risk scores were calculated based on their MastFx score at the start of treatment; in case of missing parameters, minimal and maximal MastFx scores and corresponding risks were calculated.

The BMD of the lumbar spine (anterior-posterior projection at L1-L4) and femur (total proximal femur) was measured with dual-energy x-ray absorptiometry (Hologic QDR Discovery, Waltham, Mass). Scores were established using the National Health and Nutrition Examination Survey reference database and shown as Z-score, in accordance with ISM literature.⁸ Fractured lumbar vertebrae were excluded from both baseline and 5-year BMD measurements. If the required data of separate vertebrae were lacking, BMD measurements were excluded from the analysis.

sCTX was measured in serum by electrochemiluminescence immunoassay (Elecys 2010; Roche, Mannheim, Germany; IE-CV

FIGURE 2. Fragility fracture-free survival curves of the total analyzed group (**A**, $n = 58$), the closely analyzed group with complete baseline and 5-year (± 1 year) VFA/X-ray measurements (**B**, $n = 30$), and the division between patients with high (≥ 3 , orange line) and low (< 3 , blue line) minimal MastFx scores (**C**, $n = 30$). VFA, Vertebral fracture assessment.

10.8%). Age- and gender-adjusted Z-scores were calculated as previously described.²⁸

Baseline serum tryptase levels and urinary methylhistamine (MH) and methylimidazole acetic acid levels were measured as previously described.²⁹

To assess patient compliance to bisphosphonates, the medication possession rate (MPR) was inventoried for the first 5 years of treatment. MPR was determined using medication delivery data from pharmacists. MPR $\geq 80\%$ was categorized as high compliance and $< 80\%$ as low compliance.

Statistical analysis

Baseline characteristics were expressed as the number of patients (%), mean $\pm$ standard deviation (SD) or median (interquartile range [IQR]) for categorical, normally distributed, and non-normally distributed data, respectively. The χ^2 test, Fisher exact test, independent samples *t*-test, and Mann-Whitney *U*-test were used as appropriate to compare patient characteristics between patients included and excluded in the 5-year analyses.

Five- and 10-year FFX-free survival were estimated using Kaplan-Meier survival analysis. Results were expressed as mean $\pm$ standard error (SE). The Wilcoxon-signed rank test was used to compare baseline and 5-year BMD and sCTx Z-scores. Analyses were stratified for high and low treatment compliance. *P* values $\leq .05$ were considered as statistically significant. Statistical analysis was performed with IBM SPSS Statistics 23 (SPSS, Chicago, Ill).

RESULTS

Fractures

Before bisphosphonate treatment, 37 in the total group of 58 patients had suffered 92 lifetime fractures, of which 54 were HE. Eighteen of 58 patients reported 38 FFXs, of which 34 were vertebral FFXs. One of the 18 patients had suffered both vertebral and nonvertebral FFXs. Further baseline characteristics are shown in Table I. Two women reached menopause before the age of 45 years. No other bone metabolism interfering comorbidities, for example, hypo- or hyperthyroidism, were observed.

After the start of bisphosphonate treatment with a median follow-up of 7.3 years (range, 0–12.5 years), 19 of 58 patients suffered 50 fractures, of which 10 were HE. Fourteen patients suffered 40 FFXs, all vertebral. Five- and 10-year FFX-free

survival were 81.9% (SE, 5.5%) and 67.0% (SE, 7.7%), respectively (see Figure 2, A). Patients who developed FFXs during follow-up had a significantly lower baseline femoral BMD ($P = .042$) and more frequently FFXs at baseline ($P = .004$) (see Table II). Furthermore, they more frequently had a history of anaphylaxis at baseline ($P = .028$). Neither differences in serum tryptase and urinary histamine metabolites nor in total IgE were significant.

As a tertiary referral center, only part of the patient population ($n = 30$) was under regular care in our hospital and had available baseline and 5-year (± 1 year) data on VFA and/or X-rays of the thoracolumbar spine. Their baseline characteristics were similar to those of patients without a complete set of these measurements ($n = 28$), with the exception of lower lumbar BMD and higher sCTx Z-scores (Table I). However, adequate comparison of these 2 parameters was hampered by many missing data in the group with an incomplete set of measurements.

Before bisphosphonate treatment, 17 of the 30 patients with a complete set of measurements suffered 47 lifetime fractures, of which 28 were HE. Ten patients suffered 19 FFXs, of which 17 were vertebral. One of these 10 patients suffered both vertebral and nonvertebral FFXs.

After the start of bisphosphonate treatment with a median follow-up of 7.8 years (range, 4.1–12.5 years), 12 of 30 patients suffered 27 fractures: 4 HE in 4 patients and 23 vertebral FFXs in 9 patients. One patient had both HE and FFXs. Five- and 10-year FFX-free survival were comparable to the total group, 76.5% (SE, 7.8%) and 64.8% (SE, 10.3%), respectively (Figure 2, B).

The majority of patients with FFXs suffered their first FFX within the first 5 years (measurements ± 1 year) of follow-up; 1 patient suffered the first FFX at 5.3 and 1 after 7.9 years after the start of treatment. Within the 5-year follow-up period, patients with higher (≥ 3) minimal MastFx scores showed a trend toward a higher 5-year FFX risk ($P = .166$; Figure 2, C). The mean minimal MastFx score was 2.37 (SD, 1.24) and the mean maximal MastFx score was 2.73 (SD, 1.11), corresponding with a predicted 5-year fracture risk of 33.5% (SD, 25.9%) and 38.5% (SD, 25.7%). The observed FFX risk at 5 years was 26.7%.

MPR was known for 26 of 30 patients. New FFXs during the first 5 years occurred in 4 patients with a high MPR ($n = 11$,

TABLE II. Comparison of baseline characteristics of the total included patient group (n = 58) between patients who do and do not develop FFxs under bisphosphonate treatment

Variable	FFxs under bisphosphonate treatment (n = 14)		No FFxs under bisphosphonate treatment (n = 44)		P value
	n		n		
Age at diagnosis ISM	14	55.5 (6.6)	44	51.8 (10.9)	.137
Age at the start of treatment	14	57.0 (5.4)	44	54.7 (11.4)	.291
Male gender	14	6 (42.9%)	44	21 (47.7%)	.750
Postmenopausal status women	8	7 (87.5%)	23	22 (95.7%)	.456
Urticaria pigmentosa	14	8 (57.1%)	44	28 (63.6%)	.663
History of anaphylaxis	14	10 (71.4%)	44	15 (34.1%)	.028
Body mass index (kg/m ²)	11	26.9 (2.3)	30	24.7 (4.3)	.121
Fracture history					
FFx, vertebral	14	8 (57.1%)	44	7 (15.9%)	.004
FFx, other	14	2 (14.3%)	44	2 (4.5%)	.243
HE fractures	14	7 (50.0%)	44	21 (47.7%)	>.999
Serum tryptase (μg/L)	12	44.5 (28.6 to 66.4)	39	34.1 (21.2 to 93.6)	.722
Urinary MH (μmol/mol creatinine)	13	351.0 (232.5 to 500.0)	41	298.0 (203.0 to 511.5)	.656
Urinary MIMA (mmol/mol creatinine)	12	4.3 (2.9 to 5.2)	40	3.9 (2.5 to 6.5)	>.999
Total IgE (kU/L)	14	34.80 (14.38 to 68.73)	36	18.10 (12.10 to 39.58)	.151
Baseline BMD					
Lumbar, T-score	8	−3.00 (−4.33 to −1.83)	28	−2.65 (−2.90 to −2.23)	.505
Lumbar, Z-score	8	−2.05 (−3.68 to −1.20)	28	−1.70 (−2.40 to −1.25)	.580
Femoral, T-score	11	−1.80 (−2.10 to −1.10)	26	−0.95 (−1.63 to −0.58)	.065
Femoral, Z-score	11	−1.10 (−1.70 to −0.70)	26	−0.35 (−1.10 to −0.03)	.042
Five-year change in BMD					
Lumbar, Z-score	7	1.00 (0.20 to 1.20)	20	0.65 (0.23 to 1.18)	.570
Femoral, Z-score	8	0.00 (−0.30 to 0.48)	19	0.30 (0.00 to 0.50)	.217
Baseline sCTx Z-score	9	1.77 (−0.07 to 2.88)	23	0.22 (−0.43 to 2.10)	.301
Five-year change in sCTx Z-score	6	−1.23 (−2.09 to −0.48)	9	−1.75 (−2.90 to −0.45)	.864
Use of H1 antagonists	14	5 (35.7%)	41	16 (39.0%)	.826
Use of H2 antagonists	14	3 (21.4%)	40	16 (40.0%)	.178
Alcohol	13		41		.291
Intolerance		0 (0%)		7 (17.1%)	
Tolerance		13 (100%)		28 (68.3%)	
Abuse		0 (0%)		4 (9.8%)	
Smoking status	13		42		.195
Current		6 (46.2%)		16 (38.11%)	
Quit (≥1 y)		1 (7.7%)		7 (16.7%)	
Never		6 (46.2%)		19 (45.2%)	

BMD, Bone mineral density; FFx, fragility fractures; HE, high energetic trauma; ISM, indolent systemic mastocytosis; MH, methylhistamine; MIMA, methylimidazole acetic acid; sCTx, serum collagen C telopeptide.

Bold indicates statistical significance ($P < .05$).

36.4%) and 4 with a low MPR (n = 15, 26.7%; $P = .683$). The MPR of patients with a history of FFxs at baseline was not significantly higher. Patients with a high MPR tend to be older compared with patients with a lower MPR (median, 56.9 years [IQR, 51.3–59.8] vs 53.7 years [44.8–56.5]; $P = .097$). Analyses correlating MPR as a continuous variable to FFx history at baseline, FFxs during follow-up, or 5-year change in sCTx Z-score or femoral or lumbar BMD were not significant.

Bone mineral density

Median (IQR) BMD Z-scores significantly increased from baseline to 5-year follow-up (see Figure 3). Lumbar BMD increased from −2.20 (−2.80 to −1.50) to −1.50 (−2.30 to −0.60) ($P < .001$, n = 27), femoral BMD from −0.90

(−1.20 to −0.10) to −0.50 (−1.10 to 0.10) ($P = .037$, n = 27). One osteosclerotic outlier was excluded from analysis.

The increase in lumbar BMD Z-score was significant for both high- and low-MPR patients and for both patients with and without a history of FFxs at baseline. The femoral BMD Z-score only significantly increased in patients without a history of FFxs at baseline.

Serum collagen C telopeptide

The baseline sCTx Z-score significantly decreased from median (IQR) 0.71 (−0.59 to 2.39) to −0.95 (−1.30 to −0.16) at 5-year follow-up ($P = .008$, n = 15), indicating compliance to bisphosphonate treatment (Figure 4).

FIGURE 3. Boxplots of 10th to 90th percentile for the lumbar and femoral BMD Z-score at baseline and at 5-year follow-up. The dots represent outliers. *BMD*, Bone mineral density.

FIGURE 4. Boxplot of 10th to 90th percentile for the sCTX Z-score at baseline and at 5-year follow-up. The dots represent outliers. *sCTX*, Serum collagen C telopeptide.

Adverse events

No adverse events such as osteonecrosis of the jaw or atypical femur fractures were observed.

DISCUSSION

Patients with ISM are at high risk for osteoporosis and FFxs, also at a relatively young age (<60 years). Bisphosphonates are the first line of treatment. Our study is the largest study with the longest follow-up so far to evaluate the efficacy of bisphosphonates in patients with ISM and demonstrates that the risk of FFxs in patients with these manifestations remains high despite treatment. Fourteen of 58 patients suffered 40 new FFxs, corresponding with an FFx-free survival of, respectively, 81.9% after 5 years and 67.0% after 10 years, indicating a persisting vulnerability despite treatment.

To put this vulnerability into perspective, we compared the 5- and 10-year FFx-free survival with that of patients with ISM not treated with antiosteoporotics; with respectively 77% and 69%,⁶ these are comparable. Whether bisphosphonates are effective is dependent on the pretreatment FFx risk of both populations. Either this risk is higher in the current population, meaning

bisphosphonate treatment reduces FFx, or the pretreatment FFx risk of both study populations is comparable, in which case bisphosphonates would not be effective in reducing FFx risk. The MastFx scoring system was used to compare the pretreatment FFx risk of both study populations. Unfortunately, we lacked statistical power to draw a definitive conclusion on the FFx risk reductive potential of bisphosphonates. However, because the current study population is older than the population in whom the MastFx score was developed (mean age, 55.2 ± 10.3 vs 46 ± 13 years)⁶ and because, contrary to the previously investigated population, in these patients it was decided to start treatment, a higher pretreatment FFx risk and thus some FFx risk reduction seems plausible.

Nonetheless, the FFx risk and thus the vulnerability of this relatively young population remains alarmingly high despite treatment. To exclude that this disappointingly high fracture rate is a result of incompletion to therapy, BMD and sCTX Z-score and MPR were assessed. A significant increase in BMD and a significant decrease in sCTX Z-score were found. These findings imply adequate bisphosphonate intake.^{28,30,31} The significant increase of BMD in both patients with high and low patient compliance suggests that the retrospective collection of the pharmaceutical data may have caused an underestimation of MPR.

Apparently, a significant increase in BMD and a decrease of sCTX may not be protective for new FFxs in ISM. Why does this population remain so vulnerable under bisphosphonate treatment? Risk factors for new FFxs under bisphosphonate therapy are previous vertebral FFxs, a lower baseline femoral BMD, and a history of anaphylaxis.

Low femoral BMD is a well-known risk factor for new vertebral FFxs in postmenopausal osteoporosis,^{24,32} and in a previous study by our research group, this has also been identified as a risk factor for FFxs in patients with ISM who were not treated with antiosteoporotics.⁶ Other risk factors identified in that study, male gender, alcohol use, high sCTX levels, and absence of urticaria pigmentosa, were not identified in this ISM population under bisphosphonate therapy.⁶

Also, a correlation between the history of anaphylaxis and FFxs or BMD has previously been described in ISM literature.^{6,8} Such a correlation with other clinical manifestations could imply that the mutation burden or composition of mast cell mediators plays a role in the underlying pathophysiology and might explain which patients do and do not benefit from bisphosphonate

therapy. However, current findings do not support that hypothesis as no correlation was found between serum tryptase or urinary histamine metabolite levels and the risk of new FFxs. Findings in literature are also inconclusive. The burden of KIT D816V mutation does not correlate to osteoporosis.³³ MH has previously been identified as a risk factor for bone manifestations (osteoporosis and/or FFxs)⁴ but was not found to be an independent predictor of FFxs.⁶ In previous studies, tryptase was found to be correlated with a higher BMD. This finding was particularly found in patients with more aggressive forms of mastocytosis.^{34,35} Also in patients with ISM with osteoporosis, this correlation with tryptase has been described,^{5,35} although such an association was not persistently found.^{4,8,34} No association between tryptase levels and a higher risk of fractures has been described.⁶

In summary, literature does not show a persistent risk profile when it comes to FFxs or other bone manifestations. It is striking that especially patients with previous FFxs were prone to develop more FFxs. Patients without previous fractures did usually remain free of fractures. This observation complicates the translation of the current findings into daily clinical practice. In guidelines, it has been advised to measure BMD on a yearly basis.² In this study, the BMD increase appeared to have no predictive value regarding the risk of new FFxs during bisphosphonate treatment. Therefore, it is unclear when and on which grounds a switch in therapy is indicated, especially because research on the effect of other treatment options, for example, interferon alpha or denosumab, on bone manifestations in ISM is limited.^{12,17,18}

In conclusion, our retrospective cohort study in patients with ISM shows that treatment with bisphosphonates significantly increases BMD and decreases bone resorption (sCTX), but FFxs still frequently occur. Especially, patients with ISM with previous FFxs remain at high risk of new FFxs under bisphosphonate treatment. This underlines that the disease burden remains unequivocally high in this relatively young patient population.

The findings of this study highlight the need for further prospective studies on bisphosphonates and other anti-osteoporotic therapies (eg, denosumab), as well as the effect of the addition of specific mast cell targeting therapies (eg, midostaurin) or cytoreductive treatment (eg, interferon alpha) on bone manifestations in ISM.

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