RESEARCH ARTICLE

Medication related osteonecrosis of the jaw in osteoporotic vs oncologic patients—quantifying radiographic appearance and relationship to clinical findings

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Objectives: To explore whether differences exist in the clinical and radiographic presentation of oncologic vs osteoporotic patients with medication-related osteonecrosis of the jaw (MRONJ).

Methods: We retrospectively assessed panoramic radiographs and CBCT examinations of 70 MRONJ patients receiving antiresorptive medications for the management of either osteoporosis or bone malignancy. Radiographic features of MRONJ were documented and categorized according to severity. A composite radiographic index (CRI) was constructed to account for the heterogeneity in radiographic manifestations of MRONJ and further stratify extent of osseous changes.

Results: Patients with osteoporosis were mostly older females and presented more frequently with Stage 2 MRONJ, while patients with malignancy were equally distributed between males and females, and presented mostly with Stage 1 MRONJ. Most MRONJ lesions in oncologic patients occurred in the mandible, whereas the maxilla and mandible were equally affected in osteoporotic patients. Patients with minimal radiographic changes (low CRI score) often presented with MRONJ in dentate areas, while most patients in medium and high CRI groups presented with MRONJ after recent tooth extraction. The low CRI group consisted of primarily oncologic patients, while osteoporotic vs oncologic patients were divided more evenly in the other CRI groups ($p = 0.083$). While CRI scores increased with clinical staging, a Spearman's rank correlation coefficient of 0.49 suggests that clinical appearance does not reliably predict osseous changes.

Conclusions: Our data identify differences in the MRONJ appearance of patients with osteoporosis vs malignancy and emphasize the significance of detailed radiographic assessment, in addition to the clinical appearance, in characterizing the osseous changes of the disease.

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Introduction

Osteonecrosis of the jaw (ONJ) is an infrequent but serious adverse effect associated with antiresorptive medications, including bisphosphonates and denosumab. Recently, the term medication-related ONJ (MRONJ) was introduced to describe ONJ in patients treated with medications other than antiresorptives. The American Association of Oral and Maxillofacial Surgeons (AAOMS) states that “patients may be considered to have MRONJ if all of the following characteristics are present: (1) current or previous treatment with antiresorptive or antiangiogenic agents; (2) exposed bone or bone that can be probed through an intraoral or extraoral fistula(e) in the maxillofacial region that has persisted for more than eight weeks; and (3) No history of radiation therapy to the jaws or obvious metastatic disease to the jaws”.¹

The extent and severity of MRONJ varies considerably and includes the following categories: “Stage 0”—no bone exposure, but with non-specific clinical or radiographic findings; “Stage 1”—exposed and necrotic bone, or fistulae probing to bone, in asymptomatic patients with no evidence of infection; “Stage 2”—bone exposure associated with infection; and “Stage 3”—extension of necrotic bone and infection beyond the confines of the alveolar ridge or pathologic fracture or oral–antral/oral–nasal communication or extraoral fistula.¹

Antiresorptive medications are utilized to prevent or mitigate risks associated with systemic bone loss in patients with osteoporosis and skeletal malignancy. MRONJ incidence is 1–2% in oncologic patients receiving high-dose antiresorptives, and about 100 times less in osteoporotic patients receiving lower doses.^{1,2} Dental extraction is considered the primary precipitating event for development of MRONJ. However, pulpal and periodontal inflammation, removable dental prostheses, minor mucosal trauma, and dentoalveolar surgery are also recognized as local risk factors.^{3–6} Despite heightened awareness of MRONJ, “spontaneous” cases without obvious precipitating factors are increasingly reported.^{1,7–9}

Radiographic features of sclerosis, osteolysis, periosteal reaction and sequestration reported in MRONJ patients, also represent non-specific, inflammatory changes seen in other conditions.^{7,10–12} Size of clinically exposed bone often underestimates the extent and severity of osseous changes revealed by various imaging modalities.^{7,13,14} Despite agreement that imaging is central in delineating MRONJ disease burden and can influence patient management, the utility of imaging in the evaluation of patients with MRONJ and its contribution to clinical staging remain vague.^{15,16} AAOMS 2014 guidelines advocate radiographic assessment in Stage 0 MRONJ patients, with no stated contribution to evaluation of other stages. Few studies relate MRONJ imaging findings to patient demographics, underlying

primary disease, type of antiresorptive therapy, MRONJ precipitating event, and clinical presentation.

Given the disparity of MRONJ incidence between patients with osteoporosis and bone malignancy, the objective of our study was to investigate clinical and radiographic differences between these two primary disease groups. A secondary objective was to develop a clinically practical method for quantifying radiographic MRONJ disease burden.

Methods and materials

Patient sample

Following UCLA IRB approval, dental records including demographics, dental and medical history, clinical photographs and radiographic imaging were reviewed retrospectively. 198 patient records from patients with suspected MRONJ seen at the UCLA School of Dentistry between 2010 and 2016 were reviewed. The following inclusion criteria were applied: (1) history of antiresorptive medication for treatment of osteoporosis or bone malignancy, (2) AAOMS Stage 1, 2 or 3 MRONJ at time of initial clinical presentation, and 3) two-dimensional (panoramic) and three-dimensional (cone beam CT, CBCT) “baseline” imaging (time of presentation at UCLA).¹ Patients were excluded if there was a history of head/neck radiation, bone metabolic disease other than osteoporosis, or if CBCT scan was not acquired within 6 months of patient presentation. 70 patients satisfied the inclusion and exclusion criteria. Our study conformed to the STROBE guidelines.

Analysis of patient files & imaging

Patient information, including age, sex, underlying primary disease, date of initial presentation, MRONJ clinical staging, antiresorptive medication(s), inciting event, and site and extent of bone exposure were ascertained from patient charts and clinical photographs. Clinical photographs at initial presentation were reviewed to corroborate the documented clinical staging.

Baseline panoramic radiographs and CBCT examinations were available for all patients. Imaging was reviewed under standardized viewing conditions by two examiners working in consensus: one board-certified Oral and Maxillofacial Radiologist (ST) and one senior oral and maxillofacial radiology resident (KCW). CBCT examinations were acquired with the 3D Accutomo 170 scanner (J. Morita, Irvine, California, USA), utilizing various fields of view, and corresponding high resolution reconstructions (0.125–0.250 mm voxel size).

Four radiographic parameters (sclerosis, lytic changes, periosteal reaction and sequestration) were scored as absent (0), localized (1) or extensive (2). “Localized” was defined as changes occurring within one tooth dimension mesiodistally from the site of clinical

Figure 1 Examples of radiographic index scoring for severity of sclerosis, lytic changes, periosteal reaction and sequestrum formation. Changes limited to the alveolar bone and within one mesiodistal tooth dimension from the clinical bone exposure are considered localized, while involvement beyond these boundaries is deemed extensive. Arrows in each inset point to the radiographic feature assessed.

bone exposure, and limited to alveolar bone. Changes extending beyond these boundaries were deemed “extensive.” Figure 1 demonstrates typical examples of radiographic measures. To quantitate the extent and severity of radiographic changes, a composite radiographic index (CRI) was constructed by totalling scores for each of the four radiographic parameters (sclerosis, lytic changes, periosteal reaction, sequestration), yielding a theoretical range of 0–8.

The presence/absence of generalized thickening of the lamina dura and/or non-healing extraction sockets were also recorded, as well as the presence of generalized caries, periapical and/or periodontal disease.

Data analysis

Patient characteristics were summarized using frequencies (percentages) or averages (standard deviations) unless otherwise noted. For comparing patient characteristics between osteoporotic and oncologic, we used the *t*-test for age and χ^2 or Fisher’s exact test as appropriate for categorical variables. Ordinal by ordinal associations (*e.g.* clinical stage and radiographic findings) were assessed using Spearman’s rank correlation coefficient. Statistical analyses were performed using IBM SPSS V24 (Armonk, NY) and SAS V9.4 (Cary, NC). *p*-values < 0.05 were considered statistically significant.

Results

Patient demographics—systemic disease groups

Table 1 shows the patient demographics. The analysis included a total of 70 patients (44 females and 26 males, average age 72 years). 41 patients were undergoing antiresorptive therapy for bone malignancy (16 prostate, 11 breast, 8 multiple myeloma, 6 other type) and 29 for osteoporosis. Statistically significant differences in gender and mean age between osteoporosis vs

Table 1 Demographics of the MRONJ patients

	Osteoporotic	Oncologic	Total	<i>p</i> -value
Male	2 (6.9%)	24 (58.5%)	26 (37.1%)	<0.001
Female	27 (93.1%)	17 (41.5%)	44 (62.9%)	
Mean Age	78.0	67.4	71.8	<0.001
Bisphosphonates only	22 (75.9%)	21 (51.2%)	43 (61.4%)	<0.05
Denosumab	7 (24.1%)	20 (48.8%)	27 (38.6%)	
Stage 1	8 (27.6%)	24 (58.5%)	32 (45.7%)	<0.05
Stage 2	13 (44.8%)	11 (26.8%)	24 (34.3%)	
Stage 3	8 (27.6%)	6 (14.6%)	14 (20.0%)	
Maxilla only	12 (41.4%)	9 (22.0%)	21 (30.0%)	0.067
Mandible only	15 (51.7%)	31 (75.6%)	46 (65.7%)	
Both arches	2 (6.9%)	1 (2.4%)	3 (4.3%)	
Total	29	41	70	

MRONJ, medication-related osteonecrosis of the jaw.

malignancy patients were observed ($p < 0.001$). Nearly all patients with osteoporosis were female (27F:2M), vs a more even gender distribution in the oncologic group (24F:17M). Patients with osteoporosis vs malignancy were 10.6 years older on average.

Antiresorptive medications included various bisphosphonates and/or denosumab. 43 patients reported therapy with bisphosphonates exclusively, while 27 patients reported a history of denosumab therapy exclusively or following prior treatment with bisphosphonates. Information regarding exact dosing schedules and duration of antiresorptive therapy was not available. A statistically significant difference ($p < 0.01$) in the distribution of antiresorptive medication between patients with osteoporosis vs malignancy was observed. Patients with osteoporosis were treated most often only with bisphosphonates. In contrast, 20 oncologic patients (48.8%) had undergone denosumab therapy, with or without prior bisphosphonates.

At initial presentation, 32, 24 and 14 patients were clinically diagnosed with Stage 1, 2 and 3 MRONJ, respectively. Statistical differences existed in clinical staging distribution between oncologic vs osteoporotic groups ($p < 0.05$). Most of the osteoporotic patients presented with Stage 2 MRONJ, whereas most oncologic patients displayed Stage 1 MRONJ.

Bone exposure involved the mandible in 46 (65.7%), the maxilla in 21 (30%) and both jaws simultaneously in 3 patients (4.3%). MRONJ lesions were most prevalent in the posterior sextants (87 and 91%, respectively). Most oncologic patients presented with mandibular lesions, while lesions in osteoporotic patients were divided between maxilla and mandible, although this did not reach statistical significance ($p = 0.067$). Local inciting events/risk factors were not significantly different for osteoporotic vs oncologic patients. No MRONJ lesions were adjacent to areas of periapical disease. One MRONJ lesion was adjacent to a vertical periodontal defect, and one adjacent to an implant with peri-implant bone loss. No information regarding cause of recent extractions that progressed to MRONJ lesions was available. Furthermore, clinical information

regarding active/ongoing periodontal inflammation vs stable periodontal attachment loss was not available.

Prevalence of radiographic features of MRONJ

Statistically significant differences in sclerosis ($p < 0.01$), lytic changes ($p < 0.01$), sequestration ($p < 0.001$), and periosteal reaction ($p < 0.05$) were identified between clinical stages 1, 2, and 3 (Figure 2). Sclerosis, osteolysis and sequestrum formation were frequent findings in Stage 1 and 2 MRONJ, and were universal in Stage 3 MRONJ (Figure 2a–c). Periosteal reaction, a less common finding in stages 1 and 2, was observed in over half of Stage 3 cases (Figure 2d). No statistical differences in the radiographic presence of sclerosis ($p = 0.350$), lytic changes ($p = 0.298$), sequestration ($p = 0.061$) or periosteal reaction ($p = 0.456$) were detected between osteoporotic vs oncologic patients.

Composite radiographic index (CRI)

CRI scores ranged from 0 to 8. We classified patients in three groups based on CRI scores: low CRI of 0–2, medium CRI of 3–5, and high CRI of 6–8 (Table 2). The low, medium and high CRI groups consisted of 22, 26 and 22 patients, respectively. No statistical difference was noted in CRI scores between gender groups. Older patients belonged to higher CRI groups ($p < 0.05$). The low CRI group consisted of primarily oncologic patients, while osteoporotic vs oncologic patients were divided more evenly in the medium and high CRI groups. Patients with denosumab treatment belonged mostly in the low CRI group, while patients with bisphosphonates tended to fall into the medium and high CRI groups, although this did not reach statistical significance.

Interestingly, most low CRI group patients presented with MRONJ in dentate areas, while most medium and high CRI groups patients presented with MRONJ after recent tooth extraction with a high statistical significance ($p < 0.01$). 10 of the 16 (63%) cases in dentate areas affected the lingual cortex of the posterior mandible at the mylohyoid ridge area. 8 of these 10 patients were

Figure 2 Absent, localized and extensive radiographic features of MRONJ according to clinical stage. (A) sclerosis ($p < 0.01$, Spearman's rank correlation coefficient $r_s = 0.38$), (B) lytic changes ($p < 0.01$, $r_s = 0.41$), (C) sequestration ($p < 0.001$, $r_s = 0.41$), (D) periosteal reaction ($p < 0.05$, $r_s = 0.36$). r_s : Spearman's rank correlation coefficient. MRONJ, medication-related osteonecrosis of the jaw.

Table 2 Clinical features of MRONJ patients based on CRI scores

	<i>Low CRI</i> (22)	<i>Med CRI</i> (26)	<i>High CRI</i> (22)	<i>p-value</i>
Male	8 (36%)	8 (31%)	10 (45%)	0.574
Female	14 (64%)	18 (69%)	12 (55%)	
Mean age	66 (10)	74 (10)	74 (11)	<0.05
Osteoporotic	5 (23%)	14 (54%)	10 (55%)	0.083
Oncologic	17 (77%)	12 (46%)	12 (45%)	
Bisphosphonates only	8 (36%)	19 (73%)	16 (73%)	<0.05
Denosumab	14 (64%)	7 (27%)	6 (27%)	
Maxilla only	7 (32%)	11 (42%)	3 (14%)	0.061
Mandible only	14 (64%)	13 (50%)	19 (86%)	
Both arches	1 (5%)	2 (8%)	0 (0%)	
Dentate	12 (55%)	2 (8%)	2 (9%)	0.001
Edentulous	5 (23%)	7 (27%)	8 (36%)	
Recent extraction	5 (23%)	17 (65%)	12 (55%)	
Stage 1	15 (68%)	11 (42%)	6 (27%)	<0.001
Stage 2	7 (32%)	13 (50%)	4 (18%)	
Stage 3	0 (0%)	2 (8%)	12 (55%)	
Total	22	26	22	

CRI, composite radiographic index; MRONJ, medication-related osteonecrosis of the jaw.

oncologic, and 7 of them had a low CRI score (not shown).

Finally, strong association ($p < 0.001$) between CRI groups and clinical staging was noted, with low CRI patients presenting mostly with Stage 1 MRONJ and high CRI patients presenting with Stage 3 MRONJ. Spearman's rank correlation coefficient for the association of CRI scores and clinical staging was 0.49.

Discussion

To the best of our knowledge, this represents the first study to compare MRONJ in patients with osteoporosis vs malignancy. Furthermore, it is the largest case series study to assess detailed radiographic features of MRONJ using CBCT imaging, widely utilized in clinical dentistry, and to include a significant number of patients on two antiresorptive classes (bisphosphonates vs denosumab). Our patient population was comprised of 41% osteoporotic and 59% oncologic patients. Most osteoporotic patients were females of advanced age compared to the younger oncologic patients. Because of patients with prostate cancer and, to a lesser degree, multiple myeloma, the oncologic group gender distribution was more even.

Osteoporotic patients were primarily treated with bisphosphonates. Most patients received oral, while a few patients received intravenous (i.v.) bisphosphonates. Patients treated with denosumab received subcutaneous (sc) injections. In contrast, antiresorptive treatment of the oncologic patients was evenly divided between bisphosphonates, administered i.v., and denosumab,

administered sc. Since the exact treatment regimen for our patients was not available, the potential contribution of the mode of administration could not be assessed.

MRONJ occurred slightly more than twice as frequently in the mandible than the maxilla, and uncommonly in both arches simultaneously, paralleling other large cohort studies/reviews.^{1,6,11,17} Decreased vascularity of the mandible and increased risk for trauma during mastication, particularly in the mylohyoid ridge area, have been proposed as possible factors to account for this location difference.^{17–19}

Differences were observed in initial MRONJ staging of osteoporotic vs oncologic patients. About half of the osteoporotic patients presented with Stage 2 MRONJ similar to reported findings.¹ In contrast, 58.5% of oncologic patients presented with Stage 1 MRONJ. The reason for this unexpected and interesting finding is not certain. Potentially, better education and closer monitoring of patients with malignancy, and increased awareness of the medical oncologic community lead to prevention and earlier detection. Indeed, preventive measures such as removal of hopeless teeth prior to initiating antiresorptives, meticulous oral hygiene to decrease inflammatory foci and future extractions, and atraumatic surgical technique combined with antibiotics reduce the risk of developing MRONJ.^{20–22} However, a biologic explanation accounting for this difference cannot be excluded.^{23,24} The robust osteoclastic inhibition in oncologic patients might disrupt the soft tissue-osseous interface and lead to mucosal changes with eventual bone exposure. Such patients could potentially develop Stage 1 MRONJ, without presence of infection/inflammation. In contrast, the more modest osteoclast inhibition in osteoporosis patients, combined with trauma from tooth extraction or pre-existing dental infection may lead to mostly Stage 2 MRONJ.

Three-dimensional imaging provides more detailed assessment of the extent of MRONJ changes compared to plain radiographs.^{14,25,26} CBCT, a widely available modality in dentistry, permits superior assessment of the orofacial complex, dental structures and maxillofacial pathology, and offers advantages over multidetector CT (MDCT).^{27,28} MDCT scans, ubiquitous in hospital-based settings and commonly discussed in the MRONJ literature, are usually acquired at lower spatial resolution than CBCT scans. Standard MDCT acquisition protocols include 1–3 mm axial slice thickness. Furthermore, MDCT voxels are usually anisotropic and do not facilitate coronal, sagittal or panoramic reconstructions. CBCT scans in our study, included 0.125–0.250 mm slice thickness, and isovolumetric voxels that allowed reconstruction of coronal, axial and sagittal, as well as panoramic and transaxial cross-sections for detailed assessment of all patients.

Some authors have described the utility of imaging in delineating MRONJ extension, treatment planning and monitoring.^{7,15} However, the current AAOMS staging is based mainly on clinical findings. Thus, a secondary

goal of our study was to further examine how imaging could contribute to MRONJ staging and assessment and to provide a comprehensive and reproducible radiographic evaluation of MRONJ patients.

Radiographically, MRONJ stages 1 and 2 demonstrated a similar appearance, however, significant differences in all parameters were noted for Stage 3 patients. Surprisingly, bone sclerosis was absent in 27% of the patients, a finding that contrasts with Bedogni *et al* who observed bone sclerosis in all patients.¹¹ The same study did not report on other radiographic findings, so could not be compared with our data. No differences in the presence or severity of the various radiographic parameters was detected between osteoporotic vs oncologic patients.

Individual radiographic parameters oversimplified and underestimated the heterogeneity of the radiographic manifestations of MRONJ. This led us to develop a CRI, similar to Bianchi *et al* who proposed recording the absence or presence of MRONJ radiographic attributes.⁷ Here, we expanded this concept and recorded not only the occurrence, but also the extent of changes to create an overall radiographic estimation of disease severity.

A medium or high CRI score was seen in 83% of osteoporotic patients. In contrast, 41% of oncologic patients exhibited low CRI scores. Of all 22 cases with low CRI scores, 77% were oncologic patients. This disparate distribution, although not reaching statistical significance ($p = 0.083$), paralleled the significant differences in clinical staging noted between osteoporotic vs oncologic patients, described earlier, and suggested that the milder appearance of radiographic changes in oncologic patients may reflect earlier diagnosis. Patients on bisphosphonates demonstrated higher CRI scores reflecting a more severe radiographic disease burden. These differences may reflect the much longer bisphosphonate half-life compared to denosumab.²⁹

Intriguingly, significant differences were identified among CRI scores in relation to the bone exposure site. Approximately, half (12/22) of low CRI cases occurred in dentate areas. These cases, in absence of tooth extraction or other surgical intervention are frequently referred as “spontaneous” cases of MRONJ and accounted for 24% of the total cases, in similar proportion to that reported.^{2,6–8} For 7 of these 12 patients, bone exposure localized to the mylohyoid ridge. Interestingly, the mylohyoid ridge is the most common location of oral ulceration with bone sequestration, a rare condition in healthy patients and clinically indistinguishable from MRONJ.^{2,30}

Medium and high CRI cases primarily occurred in areas of recent extraction, indicating a connection between overt radiographic changes, pre-existing infection/inflammation necessitating tooth removal, and additional trauma from extractions. Indeed, more clinicians are adopting a proactive/preventive approach,

avoiding extractions in patients taking antiresorptive medications whenever possible.²⁰

A strong association between CRI and clinical staging indicated a correlation between MRONJ clinical and radiographic appearance. This observation is in agreement with prior smaller case series but in contrast to a large, multicenter study of 799 patients reporting “poor agreement between the AAOMS staging system and CT findings in patients with osteonecrosis”.^{7,11,12,31} The majority of low CRI scores were seen in Stage 1, half of medium CRI scores to Stage 2 and most high CRI scores in Stage 3 patients. The Spearman’s coefficient of 0.49 between CRI and clinical staging was higher than the coefficient for any radiographic parameter individually, suggesting that the collective radiographic appearance might associate better with the clinical presentation than each specific radiographic component. The value of 0.49 also suggested that while the clinical and radiographic appearance are associated, they are not completely predictive of one another. 20% of Stage 1 patients had a high CRI, and 32% with Stage 2 MRONJ presented with low CRI scores. In essence, the clinical presentation can underestimate or overestimate osseous disease burden.

Figure 3 depicts two patients with osseous malignancy clinically diagnosed with Stage 1 MRONJ but drastically different radiographic manifestation. Patient A demonstrated mild erosive changes of the lingual crestal cortication and focal osteolysis, with no periosteal bone formation and no osteosclerosis. In contrast, Patient B presented extensive sclerosis, sequestration, periosteal reaction and lytic changes. Interestingly, these changes are clear on the CBCT, but indistinct on the panoramic images. Patient A had a CRI score of 2, while Patient B had a CRI score of 6. These data begin to quantify the relationship between radiographic and clinical assessment and, if supported by future studies, could inform decision making during MRONJ treatment planning and outcome prognosis.

Our study was limited by sample size. Absence of follow-up data did not allow assessment of radiographic findings with treatment outcomes. Additionally, the inter- and intraobserver reliability of CRI needs to be established to evaluate the reproducibility of radiographic assessment. We are currently performing such studies. A final limitation is the inherent qualitative nature of the radiographic and clinical scoring of MRONJ reflecting clinical reality, that does not lend itself to a more rigorous quantitative statistical analysis.

In conclusion, we observed significant differences in clinical appearance of MRONJ depending on underlying primary disease, with oncologic patients presenting earlier stage disease and a tendency toward dentate areas of the mandible. Radiographic manifestations often increased in parallel to clinical staging, but not unequivocally, confirming that imaging contributes additional information regarding osseous disease burden that the current clinical staging system does not

Figure 3 Two Stage 1 MRONJ cases with similar clinical but distinct radiographic appearance. A1 and B1 clinical photographs, A2 and B2 sections of panoramic radiographs of the affected area, A3 and B3 axial CBCT sections, and A4 and B4 coronal CBCT sections. Arrows point to area of osteolysis, arrowheads to area of osteosclerosis and double arrows to sequestration. CBCT, cone beam CT; MRONJ, medication-related osteonecrosis of the jaw.

capture. Further investigations are needed to longitudinally assess outcomes of patients based on both the clinical and radiographic severity of MRONJ, to definitively establish the contribution of imaging in the staging and management of patients with this debilitating condition.

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Statement for research involving human subjects

The research herein was performed according to the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Institutional approval of all studies was provided by the Institutional Review Board at the University of California in Los Angeles.

Disclosures

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