Contribution of Antiangiogenic Agents to the Risk of Medication-related Osteonecrosis of the Jaw in Combination with Antiresorptive Agents: Preliminary Results in a Comparative Prospective Report of 59 Oncologic Cases

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Aim: The aim of this preliminary study was to evaluate in an oncological population the association risk of antiangiogenic (AA) agents to antiresorptive (AR) agents on the incidence and the severity of medication-related osteonecrosis of the jaw (MRONJ).

Materials and Methods: In this prospective study, we reviewed the medical records and clinical variables of 59 consecutive oncologic patients who developed MRONJ. For all patients, we retrieved the following variables: age, gender, alcohol and tobacco use, type of cancer, use of corticosteroids for >3 months, history of diabetes, MRONJ staging, combination of AR and AA agents, dental history (surgery, prosthesis) or spontaneous, site of MRONJ, delay between AR and AA first intake, and MRONJ development. Patients were divided into two groups according to drugs therapy they underwent: group 1 (G1) including patients treated with AR agent alone and group 2 (G2) including patients receiving antiresorptive–antiangiogenic drugs (AR+AA). The degree and the therapeutical success were defined as primary outcomes and the number, the localization, and the delay in onset of the lesions as secondary outcomes. In order to identify predictive factors of osteonecrosis-free interval time, univariate and multivariate Cox regression was performed. Statistical tests were carried out using the IBM® SPSS® Statistics software. All reported P-values are two-tailed and were considered to be significant when less than 0.05.

Results: Among the 47 patients who received AR agent alone (group 1), the mean treatment duration before diagnosis of MRONJ was 39.2 months. In the second group (n = 12), patients developed MRONJ with a comparable mean time of 55 months (P = 0.16). According to the staging of MRONJ at the time of diagnosis, no significant difference (P = 0.736) was observed between the two groups. Moreover, the treatment applied was not statistically different in both the groups and was successful in 36.17% of the patients in group 1 and 58.33% of the patients in group 2. No statistically difference was reported in both the groups (P = 0.16). After statistical analysis, no significant difference in terms of MRONJ localization (P = 0.13) was observed. Finally, the incidence of spontaneous MRONJ was comparable in both the groups. Statistical analysis revealed that total time of treatment was the only factor associated with poor osteonecrosis-free interval.
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time (hazard ratio 0.99; \( P = 0.001 \)). Interestingly, the combination of an AA and AR agent was not a significant predictor factor of the interval time before the diagnosis of osteonecrosis. Additionally, corticosteroid use, diabetes mellitus, and dental consultation before treatment were not statistically related to poorer osteonecrosis-free interval time rates. **Conclusion:** In our preliminary study, neither the mean treatment time duration before the diagnosis of MRONJ nor the dose delivered was different in both the groups (AR vs. AR+AA). Moreover, no significant difference was observed between both the groups regarding the localization and the staging of MRONJ at the time of diagnosis. Interestingly, our results demonstrated that the risk of spontaneous MRONJ is statistically comparable in the AR and AR–AA groups. Additionally, the addition of an AA agent did not influence the treatment applied in the two groups of patients.

**Keywords:** Antiresorptive and antiangiogenic agents, osteonecrosis of the jaw, risk factors, treatment

**INTRODUCTION**

First, described by Marx[1] in 2003, medication-related osteonecrosis of the jaw (MRONJ) is an uncommon but serious condition defined by the American Association of Oral and Maxillofacial Surgery (AAOMS).[2] Pain, infection, and dysfunction of the jaws, affecting the quality of life of patients, were the main clinical symptoms.[3]

The incidence of MRONJ widely ranges from 0.028% to 18.6%,[4] depending on the treatment exposure, agents used, route of administration, and the treatment indication.

Currently, the incidence is increasing by the emergence of novel agents used in the field of osteoporosis and malignancies (such as multiple myeloma, breast cancer, and prostate cancer).

However, to date, the pathological pathways of MRONJ remain unknown. Several studies suggested that MRONJ may be secondary to alteration of bone remodeling in a skeletal structure in which microtrauma, inflammation, and mucosa damage are present.[5,6] In addition, in concordance with the antiangiogenic (AA) effect of the bisphosphonates, the vasculature has been hypothesized to play a major role in the development of MRONJ. This AA activity is supported by the fact that bisphosphonates highly decreased the vascular endothelial growth factor (VEGF).[7-10]

However, MRONJ has also been described in patients receiving other AA agents such as bevacizumab, sunitinib, imatinib, everolimus, ipilimumab, and azacitidine.[11,12] The pathogenesis seems to be related to the vascular effects associated with these drugs.

Moreover, MRONJ may also be associated with the use of antiresorptive (AR) drugs.[13] Given that the combination of AR and AA drugs is frequently recommended for the treatment of malignancies, it is essential to better characterize this association in terms of MRONJ risks and outcomes.

Indeed, because the healing process after trauma and mucosal damage requires revascularization, the association of AR and AA agents could theoretically exacerbate the incidence and the severity of MRONJ.[14] Actually, only few studies investigated this field. Among these studies, Lescaille et al.[15] demonstrated that bevacizumab had a potential negative influence on the incidence and severity of MRONJ in patients receiving zoledronic acid.

The aim of this preliminary study was to evaluate in an oncology population the association risk of AA agents to AR agents on the incidence and the severity of MRONJ.

**MATERIALS AND METHODS**

**METHODOLOGY OF THE LITERATURE REVIEW**

A systematic literature review was conducted on the following databases: Medline/PubMed, Scopus, Ovid, and Cochrane. MESH terms included “Bisphosphonate-Associated Osteonecrosis of the Jaw” AND “Angiogenesis Inhibitors.” Studies were selected based on the subsequent criteria: patients >18 years, with diagnosis of medication-related osteonecrosis of the jaw and with history of AR and AA agents. We excluded papers that are not written in English, abstracts without full text, and oral presentations.

**STUDY POPULATION**

In this prospective study, we reviewed the medical records of 59 consecutive oncologic patients who developed
MRONJ. Only patients with MRONJ as defined by the American Association of Oral and Maxillofacial Surgery (AAOMS) were included. History of head and neck radiation before osteonecrosis of the jaw, metastatic bone disease involving the maxillofacial region, cancer-free patients, and missing follow-up examinations were regarded as exclusion criteria. Finally, upon review of these criteria, 59 patients were selected for analysis.

**Clinical and biological characteristics**

For all patients, we retrieved the following variables: age, gender, alcohol and tobacco use, type of cancer, use of corticosteroids for >3 months, history of diabetes, MRONJ staging, combination of AR and AA agents, dental history (surgery, prosthesis) or spontaneous, site of MRONJ, delay between AR and AA first intake, and MRONJ development.

Clinical diagnosis of MRONJ was suggested based on a clinical examination, according to the following definition:

- history of AR intake;
- no history of radiation therapy to the jaws;
- bone exposure or bone that can be probed through an intra-oral or extra-oral fistula in the maxillofacial region that has not healed within 8 weeks after identification by a maxillofacial surgeon and for last no preceding surgical approach to the lesion.

MRONJ staging was defined based on each case description and according to the criteria of the AAOMS.

Patients were divided into two groups according to drug therapy they underwent: group 1 (G1) including patients treated with AR agents alone and group 2 (G2) including patients receiving AR+AA drugs.

The AR agents involved were bisphosphonates and denosumab. AA agents identified were bevacizumab, trastuzumab, axitinib, and everolimus.

**Follow-up and outcomes**

All patients take part in regular follow-up. Radiographic documentations were performed according to our internal unit standardized protocols and always by the same investigators. Measurements were acquired at least every 4 weeks after initial diagnosis. Therapeutic success was defined by the absence of pain, bone exposure of signs of infection at the bone site. At every consultation, infection was thoroughly evaluated by the assessment of swelling, redness, bleeding on probing, and purulent discharge. To determine any possible underlying progression of the disease, quarterly cone beam computed tomography scans were acquired from the affected region of interests and evaluated for necrosis progress, osteolysis, sequestrum, and pathologic fracture. Stage shifts were thoroughly documented.

**Statistical analysis**

Descriptive statistics (such as age, sex, alcohol and tobacco use, and so on) are summarized using numbers and percentages. Regarding continuous variables, means with standard deviation (SD) and medians with interquartile range (IQR) were presented for statistical analysis. The Shapiro–Wilk test was used to detect significant deviation from normality when continuous variables were used. In order to evaluate differences between the two groups (AR group and AR–AA group), Student’s t-test, Mann–Whitney test, χ² test, or Fisher’s exact test were performed as appropriate.

The univariate and multivariate Cox regression analyses were conducted to assess the association between initial variables and osteonecrosis-free interval time.

Statistical tests were carried out using the IBM® SPSS® Statistics software. All reported P-values are two-tailed and were considered to be significant when less than 0.05.

**Results**

**Patients’ characteristics**

Clinical and treatment characteristics are summarized in Table 1. Medical records of the 59 patients were included in this study. Among them, 47 patients received AR agents alone (group 1) and 12 patients received AR and AA agents (group 2). The majority of patients received zoledronate as a first AR agent (69.49%). Bisphosphonates were administrated intravenously and denosumab was injected subcutaneously. Nine of the 12 patients treated with AR + AA agents were females. In group 2 (AR + AA agents), eight patients had breast cancer, two of them had kidney cancer, one of them had multiple myeloma, and the last one had colorectal cancer. The AA agents dispensed were trastuzumab (n = 4), mTOR inhibitor (n = 2), bevacizumab (n = 1), l contraceptable, lenalidomide (n = 1), and tyrosine kinase inhibitor (n = 3).

The mean age of the patients was 64.4 and 62.25 years in group 1 (AR agents) and group 2 (AR and AA agents), respectively. Alcohol and tobacco use was more frequent in group 1 (P = 0.01). Regarding the use of corticosteroids, long-term use (> 3 months) was comparable in both the groups (P = 0.62). The incidence of diabetes mellitus was the same in both the groups (P = 0.62) [Table 2].

**MRONJ characteristics**

Among the 47 patients who received AR agent alone (group 1), the mean treatment duration before diagnosis
of MRONJ was 39.2 months. In the second group, 12 patients developed MRONJ with a comparable mean time of 55 months ($P = 0.16$).

Regarding the staging of MRONJ at the time of diagnosis, no significant difference ($P = 0.74$) was observed between the two groups. The majority of patients were affected by a stage 2 MRONJ (42.55% and 50% in group 1 and in group 2, respectively).

The treatment applied was not statistically different in both the groups. All patients received oral rinse with or without oral antibiotics. Surgery was performed in 10 patients.

Moreover, the treatment was successful in 36.17% of the patients (group 1) and 58.33% of the patients (group 2). No statistically difference was reported in both the groups ($P = 0.16$).

In order to characterize the localization of MRONJ lesions, we defined the following parameters: maxillary localization only, mandibular lesions, and lesions on both sites. Statistical analysis did not reveal significant difference in terms of localization ($P = 0.13$) in both the groups.

Finally, we recorded the incidence of spontaneous MRONJ in both the groups. In the AR-treated patients, 23 of 47 patients (48.94%) did not experience dental history and were considered as spontaneous MRONJ. The incidence of spontaneous MRONJ seemed to be comparable in the AR + AA group (5 of 12 patients (41.67%)) ($P = 0.75$).

### Table 1: Patient’s characteristics

| Variable                          | n (%), mean (SD) | Treatment             | P-value |
|-----------------------------------|------------------|-----------------------|---------|
|                                  |                  | AR (n=47)             | AR + AA (n=12) |
| Total number of patients          | 59 (100)         | 47 (79.66)            | 12 (20.34)     |
| Age (years)                      |                  | 64.4 (9.59)           | 62.25 (6.55)   | NS      |
| Gender                           |                  |                       |               |
| Male                             | 20 (33.9)        | 17 (85)               | 3 (15)        | 0.01    |
| Female                           | 39 (66.1)        | 30 (76.92)            | 9 (23.08)     |         |
| Alcohol use                      |                  |                       |               |
| Yes                              | 33 (55.93)       | 21 (63.64)            | 12 (36.36)    |         |
| No                               | 26 (44.07)       | 26 (100)              | 0 (0)         |         |
| Tobacco use                      |                  |                       |               |
| Yes                              | 18 (30.51)       | 18 (100)              | 0 (0)         | 0.01    |
| No                               | 41 (69.49)       | 29 (70.73)            | 12 (20.34)    |         |
| Disease                          |                  |                       |               |
| Breast                           | 33 (55.93)       | 25                    | 8             | 0.02    |
| Kidney                           | 2 (3.39)         | 0                     | 2             |         |
| Colon                            | 1 (1.69)         | 0                     | 1             |         |
| Multiple myeloma                 | 8 (13.56)        | 7                     | 1             |         |
| Prostate                         | 12 (20.34)       | 12                    | 0             |         |
| Bladder                          | 1 (1.69)         | 1                     | 0             |         |
| NSCLC                           | 1 (1.69)         | 1                     | 0             |         |
| Thyroid                          | 1 (1.69)         | 1                     | 0             |         |
| Corticosteroid (> 3 mo)          |                  |                       |               |
| Yes                              | 20 (33.9)        | 16 (80)               | 4 (20)        | NS (0.62) |
| No                               | 39 (66.1)        | 31 (79.49)            | 8 (20.51)     |         |
| Diabetes                         |                  |                       |               |
| Yes                              | 7 (11.86)        | 5 (71.43)             | 2 (28.57)     | NS (0.62) |
| No                               | 52 (88.14)       | 42 (80.77)            | 10 (19.23)    |         |
| Antiresorptive agent             |                  |                       |               |
| Zoledronate                      | 41 (69.49)       |                       |               |
| Pamidronate                      | 5 (8.47)         |                       |               |
| Ibandronate                      | 4 (6.78)         |                       |               |
| Alendronate                      | 2 (3.39)         |                       |               |
| Clodronate                       | 1 (1.69)         |                       |               |
| Denosumab                        | 6 (10.17)        |                       |               |

Data written in boldface mean that $P$-values were statistically significant

SD = standard deviation, AA = antiangiogenic, AR = antiresorptive, NS = non-significant, NSCLC = non-small cell lung carcinoma, Mo = months
Predictors of Osteonecrosis-Free Interval Time

Univariate and multivariate Cox regression analysis was performed to identify predictive factors of osteonecrosis-free interval time. After analysis of the 59 oncologic patient characteristics, univariate analysis [Table 3] revealed that total time of treatment was the only factor associated with poor osteonecrosis-free interval time (hazard ratio 0.99; \( P = 0.001 \)). Interestingly, the combination of an AA and an AR agent was not a significant predictor factor of the interval time before the diagnosis of osteonecrosis. Additionally, corticosteroid use, diabetes mellitus, and dental consultation before treatment were not statistically related to poorer osteonecrosis-free interval time rates.

Discussion

Nowadays, the pathophysiology of MRONJ remains poorly understood. The vast majority (> 90%) of cases occurs in the oncology patient population receiving high doses of intravenous bisphosphonates or subcutaneous denosumab\(^{16,17}\). The incidence appears to be related to dose and duration exposure. Actually, MRONJ is a multifactorial disease, and many factors have been

### Table 2: Medication-related osteonecrosis characteristics

|                        | Total (n = 59) | AR (n = 47) | AR + AA (n = 12) | P-value |
|------------------------|---------------|------------|-----------------|---------|
| **Total number of patients** | 59 (100)     | 47 (79.66) | 12 (20.34)     | NS (0.16) |
| **Time delay of diagnosis** | 39.2 (28.7) | 55 (50.4)  | 55 (50.4)     | NS (0.3)  |
| **Total time of treatment** | 41.2 (29.7) | 58.3 (52.8) | 58.3 (52.8)   | NS (0.74) |

### Staging MRONJ

| Stage | Total (n = 59) | AR (n = 47) | AR + AA (n = 12) | P-value |
|-------|---------------|------------|-----------------|---------|
| 1     | 15 (25.42)    | 13 (27.66) | 2 (16.67)       | NS (0.16) |
| 2     | 26 (44.06)    | 20 (42.55) | 6 (50)          | NS (0.13) |
| 3     | 18 (30)       | 14 (29.79) | 4 (33.33)       | NS (0.41) |

### Treatment

| Type              | Total (n = 59) | AR (n = 47) | AR + AA (n = 12) | P-value |
|-------------------|---------------|------------|-----------------|---------|
| **Medical**       | 49 (83.05)    | 40 (85.11) | 9 (75)          | NS (0.16) |
| **Medical and surgical** | 10 (16.95) | 7 (14.89)  | 3 (25)          | NS (0.75) |

### Healing

| Status | Total (n = 59) | AR (n = 47) | AR + AA (n = 12) | P-value |
|--------|---------------|------------|-----------------|---------|
| **Yes** | 24 (40.68) | 17 (36.17) | 7 (58.33)       | NS (0.16) |
| **No**  | 35 (59.32)   | 30 (63.83) | 5 (41.67)       | NS (0.75) |

### Site of MRONJ

| Location             | Total (n = 59) | AR (n = 47) | AR + AA (n = 12) | P-value |
|----------------------|---------------|------------|-----------------|---------|
| **Maxillary**        | 23 (38.98)    | 20 (42.55) | 3 (25)          | NS (0.16) |
| **Mandibular**       | 30 (50.85)    | 24 (51.06) | 6 (50)          | NS (0.75) |
| **Both**             | 6 (10.17)     | 3 (6.38)   | 3 (25)          | NS (0.75) |

### Dental history

| History             | Total (n = 59) | AR (n = 47) | AR + AA (n = 12) | P-value |
|---------------------|---------------|------------|-----------------|---------|
| **Yes**             | 31 (52.54)    | 24 (51.06) | 7 (58.33)       | NS (0.16) |
| **No**              | 28 (47.46)    | 23 (48.94) | 5 (41.67)       | NS (0.75) |

**SD** = standard deviation, **AA** = antiangiogenic, **AR** = antiresorptive, **NS** = non-significant, **MRONJ** = medication-related osteonecrosis of the jaw

### Table 3: Medication-related osteonecrosis-free interval time, after univariate and multivariate Cox regression analyses

| Variables                        | Univariate analysis | Multivariate analysis |
|----------------------------------|---------------------|-----------------------|
|                                  | HR  | 95% CI     | P         | HR  | 95% CI     | P         |
| Age                              | 1.00| 0.97–1.03  | NS        | —   | —          | —         |
| Gender                           | 0.98| 0.75–1.3   | NS        | —   | —          | —         |
| Alcohol use                      | 1.19| 0.69–2.05  | NS        | —   | —          | —         |
| Tobacco use                      | 0.97| 0.55–1.7   | NS        | —   | —          | —         |
| Corticosteroid (> 3 mo)          | 1.2 | 0.7–2.08   | NS        | —   | —          | —         |
| Diabetes                         | 1.8 | 0.8–4.04   | NS        | —   | —          | —         |
| Antiangiogenic agent             | 0.70| 0.32–1.28  | NS        | —   | —          | —         |
| Total time of treatment          | 0.99| 0.98–0.99  | **0.001** | 0.99| 0.98–0.99  | **0.001** |
| Consultation before              | 0.67| 0.3–1.48   | NS        | —   | —          | —         |
| Oral hygiene                     | —   | —          | —         | —   | —          | —         |

Data written in boldface mean that P-values were statistically significant

**HR** = hazard ratio, **CI** = confidence interval, **NS** = non-significant, **Mo** = months
identified. These include the presence of periodontal disease, oral surgical procedures with extractions or implants, radiation therapy, chemotherapy, smoking, diabetes, and glucocorticoid use.

Because the inhibition of capillary angiogenesis has been suggested as a cause of MRONJ, AA therapies have been suspected to play a major role in the development of the disease. However, nowadays, MRONJ induced by AA agents is very rare and only a few cases are reported in the literature. Nevertheless, the hypothesis that the combination of AR drugs and AA agents could enhance vascularization is reported in the literature with an increase in the number of MRONJ.

In our study, after analysis of 59 consecutive oncologic patient characteristics, the total time of treatment was the only factor associated with poor osteonecrosis-free survival. Neither the mean treatment time duration before diagnosis of MRONJ nor the dose delivered was different in both the groups (AR vs. AR+AA). Moreover, no significant difference was observed between both the groups regarding the staging of MRONJ at the time of diagnosis. Our results were in accordance with the findings published in the literature, reporting that the combination of AR and AA agents increases the development of MRONJ.

Moreover, as confirmed by the same authors, our statistical analysis revealed no significant difference in terms of localization between both the groups.

Surprisingly, the occurrence rate of MRONJ in oncologic patients with no history of dental extraction was statistically the same in both the groups. Previously, Lescaille et al. reported that the combination of AA and AR agents could predispose to the development of spontaneous MRONJ, despite good oral hygiene.

As described in the literature, AA agents are supposed to antagonize the healing process of the mucosa and increase bone exposure. As bisphosphonates have been reported to possess an AA activity, the combination of AA and AR agents seems to be able to lead potentially to a more advanced stage of the disease. However, in our preliminary study, no differences in terms of MRONJ staging were observed between the two groups (AR vs. AR+AA). In both the groups, the majority of lesions were staged 2 (42.6% and 50% in groups 1 and 2, respectively). Our results confirm the results previously reported in the literature.

Additionally, the addition of an AA agent did not influence the treatment applied in the two groups of patients. The management of MRONJ was the same in both the groups and consisted of a conservative approach in the majority of the cases. Furthermore, the treatment was successful in 36 (17%) and 58 (33%) patients in groups 1 and 2, respectively.

The treatment of MRONJ is generally difficult. For this reason, especially in a population with patients with bone metastases in which AR (and AA) agents are often recommended, prevention is even more important. Moreover, it remains obvious that the multidisciplinary team approach including a dentist, an oncologist, and a maxillofacial surgeon to evaluate and decide the best therapy for the patients is necessary.

Furthermore, in our preliminary study, the association between AA and AR agents does not seem to increase the incidence of the severity of MRONJ.

Acknowledgement
This research received no external funding.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

Authors contributions
Not applicable.

Ethical policy and institutional review board statement
The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee.

Patient declaration of consent
Informed consent was obtained from all subjects involved in the study.

Data availability statement
Not applicable.

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