

Effects of zoledronic acid on tumor growth, tumor-induced bone loss and bone pain in preclinical models of breast and prostate cancer bone metastasis and multiple myeloma bone disease

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Poster number:
Sun-100



Introduction

Bone metastases are a significant clinical problem in many major cancers, especially in breast and prostate cancer where 70-90% of advanced patients develop bone metastases. Myeloma bone disease is associated with similar clinical problems than bone metastases, including increased risk of fractures and bone pain that decrease the quality of life. The standard-of-care (SOC) to support bone health of patients is either zoledronic acid or denosumab.

In this study, we established triple-negative breast cancer (TNBC) and castration-resistant prostate cancer (CRPC) bone metastasis models, and a multiple myeloma (MM) bone disease model in our Bone Metastasis Technology Platform (BMTP) and studied efficacy of the SOC zoledronic acid in the models.

Materials and Methods

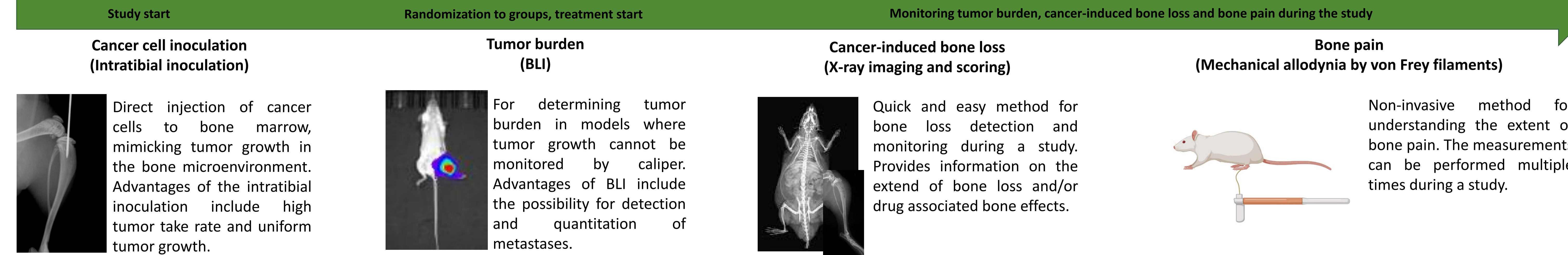
The TNBC model included 4T1 mouse TNBC cells in BALB/c mice, the CRPC model included RM-1 mouse androgen-insensitive prostate cancer cells in C57BL/6 mice, and the MM model included human RPMI 8226 cells in immunodeficient NPG mice.

In all models, luciferase-labelled cancer cells were inoculated intratibially into the bone marrow to model tumor growth in bone. Tumor growth was monitored by bioluminescence imaging (BLI) and cancer-induced bone changes by X-ray imaging. In the TNBC and CRPC models, bone pain was assessed by Von Frey filaments (mechanical allodynia).

Zoledronic acid treatment (0.1 mg/kg, QW) was started at day 3 or 4 after the cancer cell inoculation and the studies were completed at 3 weeks in the TNBC model, 4 weeks in the CRPC model, and 8 weeks in the MM model.

Results

Overview of the Bone Metastasis Technology Platform (BMTP)



Conclusions

In the preclinical models of TNBC and CRPC bone metastasis and MM bone disease, treatment with the SOC zoledronic acid resulted in strong inhibition of cancer-induced bone loss but no effects on tumor growth. Interestingly, the decreased cancer-induced bone loss did not affect bone pain, indicating that tumor growth in the bone marrow is a significant factor in the sensation of pain.

We conclude that BMTP is a clinically relevant translational tool showing the same clinical features that are observed in bone metastatic or MM bone disease patients.

Zoledronic acid can be used as a reference compound or a potential combination partner in preclinical studies where efficacy of novel therapies on bone metastases is tested, and BMTP provides a useful translational tool for evaluating efficacy of therapies on bone metastasizing cancers.

References

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TNBC bone metastasis model

In the 4T1 TNBC model, 100% of the mice had bone metastases at day 4, and maximum study duration was 21 days. Osteolytic bone lesions were clearly observed and bone pain was detected at day 7. Zoledronic acid decreased cancer-induced bone loss but had no effect on tumor growth or bone pain.

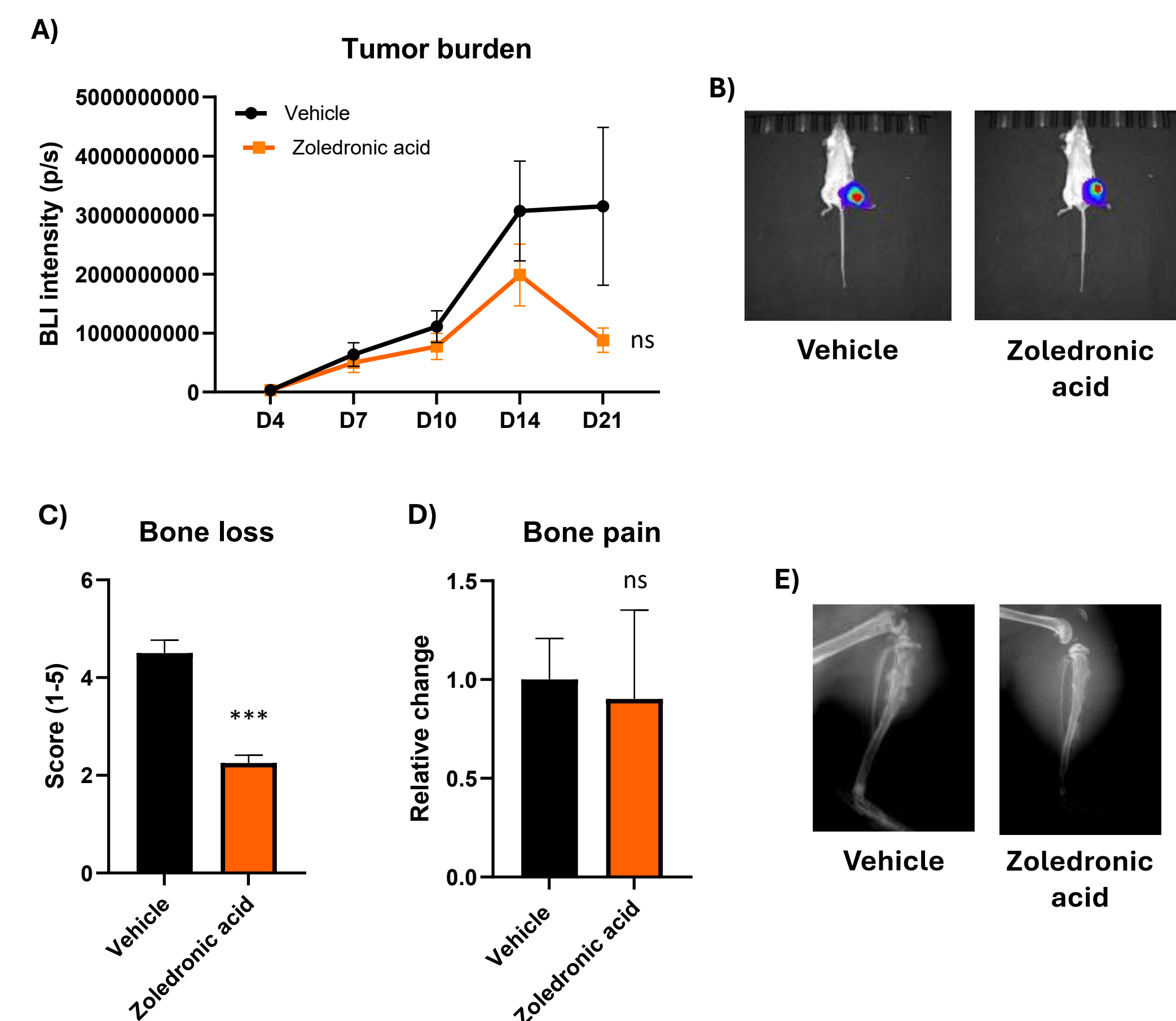


Figure 1: A) Evaluation of tumor burden by BLI for the duration of the study (mean ± SEM). B) Representative BLI images at day 21. C) Evaluation of bone loss by scoring X-ray images (mean ± SEM). D) Bone pain evaluation (mean ± SEM). E) Representative X-ray images at day 21.

CRPC bone metastasis model

In the RM-1 CRPC model, 100% of the mice had bone metastases at day 7, and maximum study duration was 28 days. Bone pain was observed at day 7, and osteolytic-mixed bone metastases were visible at day 14. Zoledronic acid decreased cancer-induced bone loss but had no effect on tumor growth or bone pain.

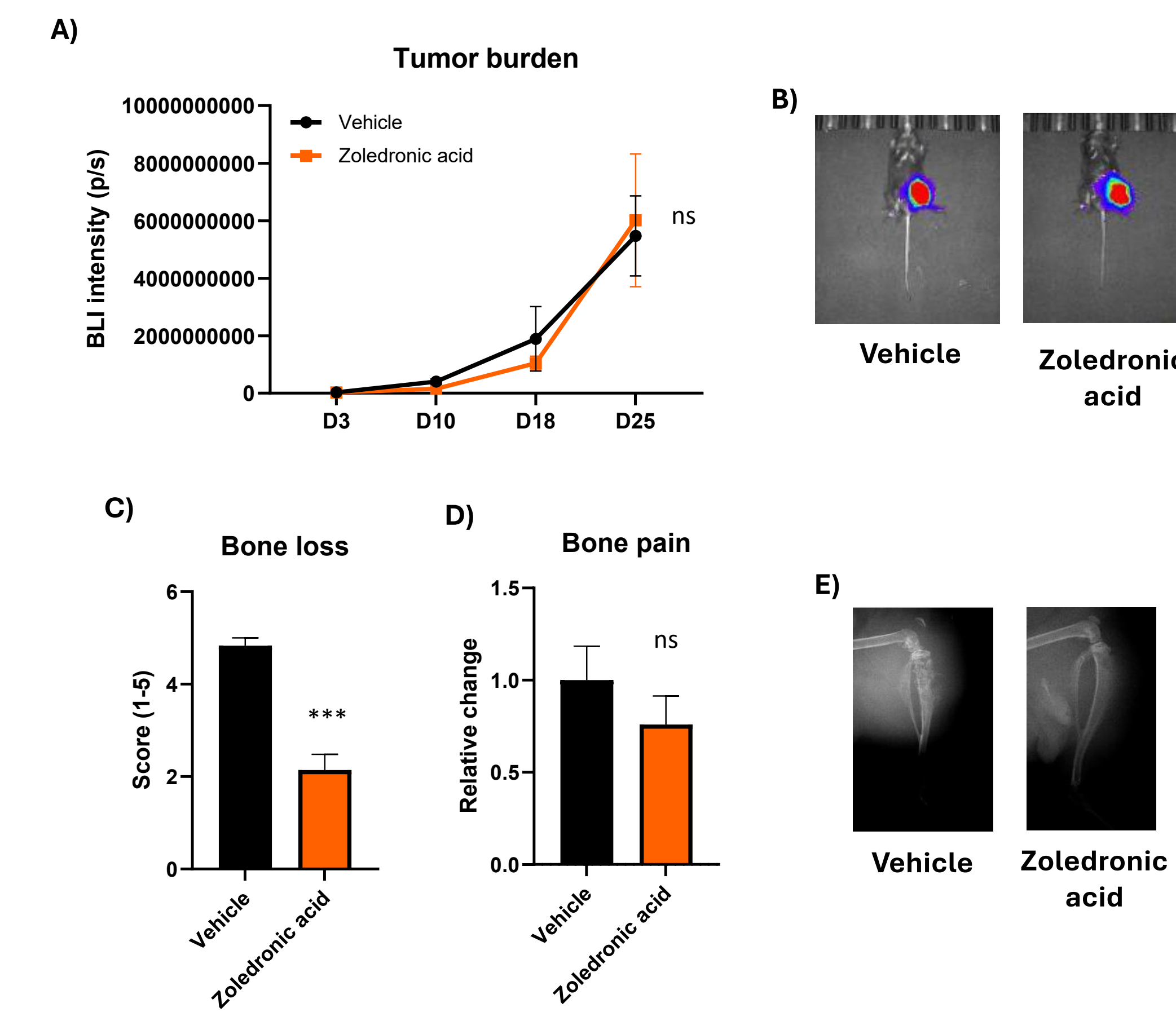


Figure 2: A) Evaluation of tumor burden by BLI for the duration of the study (mean ± SEM). B) Representative BLI images at day 25. C) Evaluation of bone loss by scoring X-ray images (mean ± SEM). D) Bone pain evaluation (mean ± SEM). E) Representative X-ray images at day 25.

MM bone disease model

In the RPMI 8226 MM model, 100% tumor take rate was detected at day 7. Osteolytic bone metastases were visible at day 21, and maximum study duration was 56 days. Zoledronic acid decreased cancer-induced bone loss but had no effect on tumor growth.

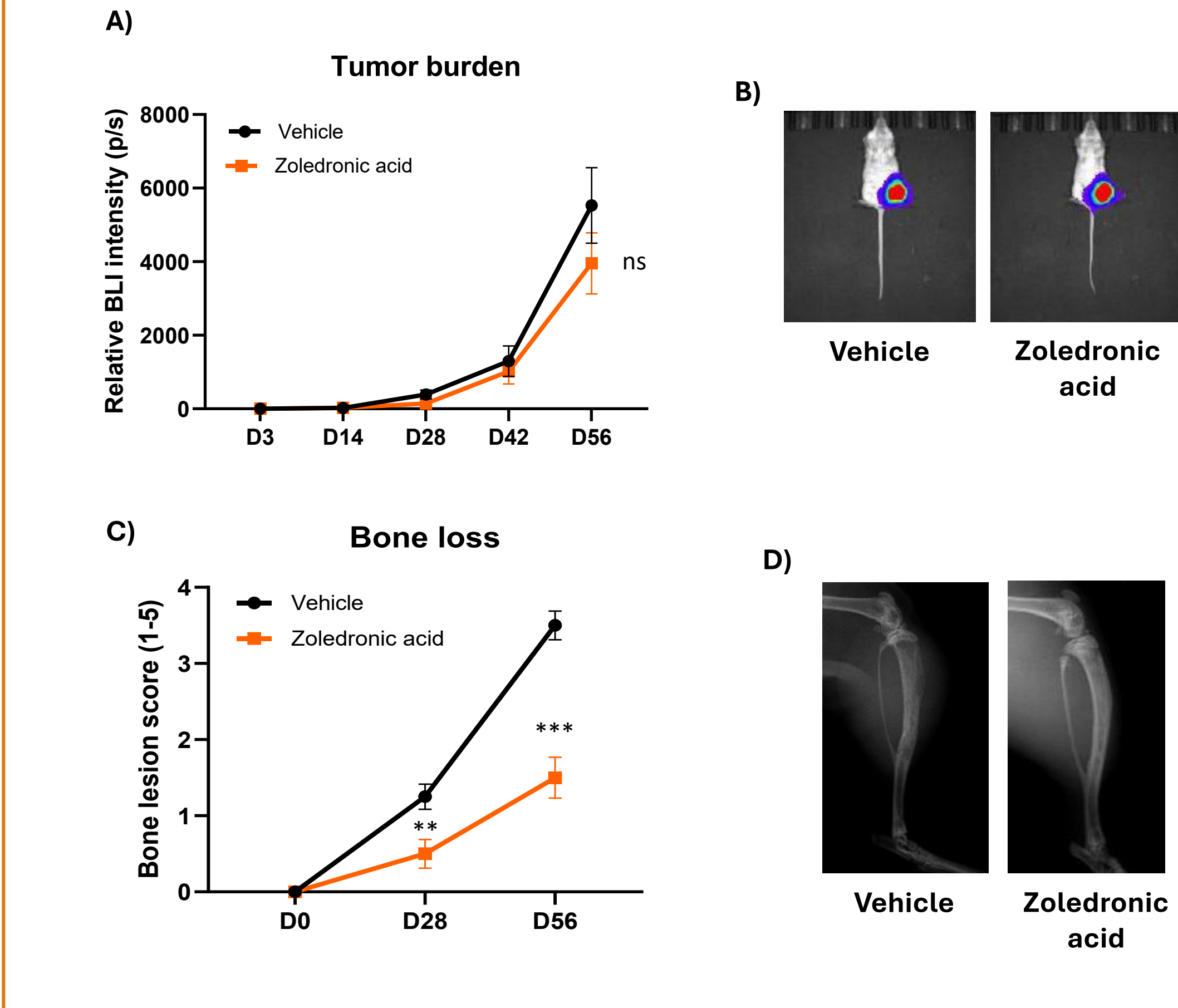


Figure 3: A) Evaluation of tumor burden by BLI for the duration of the study (mean ± SEM). B) Representative BLI images at day 56. C) Evaluation of bone loss by scoring X-ray images (mean ± SEM). D) Representative X-ray images at day 56.