INPLASY PROTOCOL

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All the authors involved in the research have no conflict of interest.

A systematic review of metastatic osteonecrosis of the jaws (MOJ) in patients undergoing antiresorptive and/or antiangiogenic therapy for skeletal-related adverse events

Sacco, R[1].

Review question / Objective: **Is there any evidence that malignant cells or metastatic cancer can be present within osteonecrosis of the jaws in patients treated with antiresorptive and/or antiangiogenic medications? - Population (P): any oncology patients previously or under treatment with antiresorptive and/or antiangiogenic drugs - Interventions (I): any type of intervention performed to treat MRONJ. - Comparison (C): no applicable - Outcome (O): state of knowledge regarding incidence of malignant cells in osteonecrosis surgical specimens; the types of antiresorptive or antiangiogenic drug, dose and rate of recurrence/ progression after treatment.**
Information sources: **The sources of the search will be PubMed, MEDLINE, EMBASE and CINAHL. The restriction will be on data obtained from January 2003.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 04 August 2020 and was last updated on 04 August 2020 (registration number INPLASY202080011).

INTRODUCTION

Review question / Objective: **Is there any evidence that malignant cells or metastatic cancer can be present within osteonecrosis of the jaws in patients treated with antiresorptive and/or antiangiogenic medications? - Population (P): any oncology patients previously or under treatment with antiresorptive and/or**

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Rationale: There is a lack of understanding of metastatic cancer and their implication/ incidence in MRONJ affected patients.

Condition being studied: At present MRONJ is a poorly understood pathological process. Several hypotheses related to the pathophysiology of MRONJ have been suggested, however this mechanism is also dependent on the specific antiresorptive and/or antiangiogenic drug therapy. The most accredited hypothesis of the pathophysiology of MRONJ is thought to be a due to a combination of suppression of osteoclastic activity; anti-angiogenesis, infection and genetic susceptibility . Among the patients unfortunately affected by MRONJ, a number of cases have demonstrated the presence of both malignant cells and metastatic spread from primary cancers. Malignant tumors can secrete a range of cytokines that allow them to be self-regulated, maintaining their own blood supply and proliferation. Therefor metastatic and primary bone cancers all have an ability to cause or contribute to osteonecrotisis of the jaws.

METHODS

Participant or population: Any oncology patients previously or under treatment with antiresorptive and/or antiangiogenic drugs.

Intervention: Any type of intervention performed to treat MRONJ.

Comparator: No applicable.

Study designs to be included: Prospective cohort, retrospective cohort, case report, case series, controlled clinical trial, and (RCTs).

Eligibility criteria: The type of studies included in the research strategy were published or unpublished randomised controlled trials, case-controlled trials, case series, retrospective studies and case reports.

Information sources: The sources of the search will be PubMed, MEDLINE, EMBASE and CINAHL. The restriction will be on data obtained from January 2003.

Main outcome(s): The current state of knowledge regarding the frequency of cancer present in osteonecrotic sites within the jaw in patients receiving antiresorptive and/or antiangiogenic medications.

Additional outcome(s): Evaluate the contributing factors to the MRONJ: The most common cancer phenotype found within the osteonecrotic sample; Triggering cause; Site of the MRONJ; The frequency of complications related to the treatment of the MRONJ and reoccurrence of MRONJ.

Quality assessment / Risk of bias analysis: Two review authors will appraise the risk of bias in the included study with the tool recommended by the Cochrane Handbook for Systematic Reviews of Interventions as appropriate for randomised control trials (RCTs). The authors will use the consensus-based clinical case reporting guidelines development (CARE checklist) for case reports and the NIH 2014 (National Institute of Health – Quality Assessment Tool for Studies) checklist for the case series/longitudinal studies . Any disagreements in risk of bias assessments will be referred to another author of the review team and subsequently resolved by discussion. Levels of evidence were assessed according to the levels of evidence for therapeutic studies adapted from the American Society of Plastic Surgeons.

Strategy of data synthesis: This systematic review will no adopt any restriction on minimum number of studies or heterogenicity of the studies. In case of heterogenicity of the cohort of patients and

studies a descriptive statistic will be used to analyse and present the data.

Subgroup analysis: We anticipate that potentially few patients affected by metastatic osteonecrosis of the jaw. However it is little known about the success in treating this patients. We also anticipate that the data for such a rare condition are little and heterogenic. Hence the statistic analysis will be more likely to be descriptive.

Sensibility analysis: If sufficient data are extracted, a sensitivity analysis will be conducted to check the stability of the outcome results by excluding low methodological quality or high risk of bias studies.

Country(ies) involved: United Kingdom.

Keywords: Medication-related osteonecrosis of the jaw; Skeletal-related events; jaw bone metastasis; cancer; antiresorptive drugs; antiangiogenic drugs.

Contributions of each author:
Author 1 - Roberto Sacco.