INPLASY PROTOCOL

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

The role of antiresorptive drugs and medication related osteonecrosis of the jaw in non-oncologic immunosuppressed patients: a systematic review

Sacco, R[1].

Review question / Objective: **Is there any sufficient evidence that non-oncology immunosuppressed patients are at higher risk of developing osteonecrosis of the jaws (ONJ) due to antiresorptive drug therapy? (PICOS strategy) Population (P): Any non-oncology immunosuppressed patients previously or under treatment with antiresorptive drugs. Interventions (I): any type of intervention performed to treat MRONJ. Comparison (C): no applicable. Outcome (O): state of knowledge regarding risk of medication related osteonecrosis of the jaw as it relates to type of drug, dose, time-to-event and rate of recurrence/progression after treatment in the immunosuppressed category of patients. Study design (S): Prospective cohort, retrospective cohort, case report, case series, controlled clinical trial, and (RCTs).**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 31 May 2020 and was last updated on 31 May 2020 (registration number INPLASY202050114).

INTRODUCTION

Review question / Objective: **Is there any sufficient evidence that non-oncology immunosuppressed patients are at higher risk of developing osteonecrosis of the jaws (ONJ) due to antiresorptive drug therapy? (PICOS strategy) Population (P): Any non-oncology immunosuppressed patients previously or under treatment with antiresorptive drugs. Interventions (I): any type of intervention performed to treat MRONJ. Comparison (C): no applicable. Outcome (O): state of knowledge regarding risk of medication related osteonecrosis of the jaw as it relates to type of drug, dose, time-to-event and rate of recurrence/progression after treatment in the**

immunosuppressed category of patients. Study design (S): Prospective cohort, retrospective cohort, case report, case series, controlled clinical trial, and (RCTs).

Condition being studied: The medical term medication-related osteonecrosis of the jaws (MRONJ) defines a severe condition that is caused by using specific medications, such as antiangiogenic or antiresorptive drugs. These medications are used for the treatment of skeletal manifestation of many diseases included benign (osteoporosis) and malignant (bone metastasis) . Researches have reported that for patients treated with intravenous bisphosphonates the incidence of MRONJ following tooth extraction is expected to range from 1.6-14.8% and 1.3-15.6% for those receiving denosumab, while 0.5% for patients taking oral bisphosphonates. In addition to the signs, symptoms and incidence of MRONJ; clinicians and surgeons need to be aware of the risk factors that can contribute to the development and severity of the condition. The exposure to antiresorptive and antiangiogenic therapy represents the primary risk factor for MRONJ; however, it has been established that MRONJ can be affected by other local and systemic factors. In the current literature, MRONJ has been associated with and accelerated by certain medical conditions, for example the presence of anemia; diabetes-mellitus, diseases of immunosuppression and renal failure, increase the incidence of MRONJ. However it remains unclear whether these concomitant diseases or conditions are distinct contributing factors.

METHODS

Participant or population: The review considers studies involving non-oncologic and immunosuppressed patients who developed MRONJ. No restriction of age, gender or ethnic origin will be applied.

Intervention: Any type of intervention intends to treat the MRONJ (e.g conservative, sequestrectomy, resection) in this particular category of patients.

Comparator: Not 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 risk of medication related osteonecrosis of the jaw as it relates to type of drug, dose, time-to-event and rate of recurrence/progression after treatment in the immunosuppressed category of patients.

Additional outcome(s): Evaluate the contributing factors to the MRONJ such as: Invasive dental procedures; Unfit dental prosthesis; Spontaneous event; Site of the necrosis (maxilla, mandible, anterior or posterior of the jaws); Rate of complications related to the disease (fracture of the jaws, sepsis etc) and to the treatment of the disease (intra or post-operative complications).

Quality assessment / Risk of bias analysis: Two people 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). Moreover, the same people will use the consensus-based clinical case reporting guidelines development (CARE checklist) for case reports and the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology). Any disagreements in risk of bias assessments will be resolved by discussion.

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: There will be no subgroups.

Sensibility analysis: We anticipate that potentially the patient affected by immunosuppressed disease are more prone to develop MRONJ. 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.

Language: Any language, no restriction.

Country(ies) involved: United Kingdom.

Keywords: osteonecrosis; medication related osteonecrosis of the jaw; antiresorptive drugs; immunosuppress; patients; intervention.

Contributions of each author:
Author 1 - Roberto Sacco.