1. ABSTRACT

- **Title**

Occurrence of serious infection among patients with rheumatoid arthritis or psoriatic arthritis concurrently exposed to an immunosuppressive biologic and denosumab: US physician practice chart review study.

- **Keywords**

Retrospective, chart review, electronic medical charts

- **Rationale and Background**

Denosumab (Prolia®) is a fully human monoclonal antibody that inhibits the binding of RANK ligand (RANKL) to RANK on osteoclasts, thereby reducing bone resorption. Denosumab is a treatment option for reducing risk of osteoporosis-related fracture among men and postmenopausal women with osteoporosis who are at high risk for fracture, as well as non-metastatic prostate cancer patients receiving androgen deprivation therapy and female breast cancer patients receiving adjuvant aromatase inhibitor therapy who are at high risk for fracture.

Rheumatoid arthritis (RA) and psoriatic arthritis (PsA) are autoimmune diseases that contribute to the risk of osteoporosis and fracture. Denosumab may be an appropriate therapy for some patients with these conditions. Rheumatoid arthritis, as well as many of the treatments for RA and PsA, are associated with an increased risk of serious infection, particularly of the pulmonary system and skin or soft tissues. Although the etiology of this increased infection risk is not yet well understood, immunosuppressive biologic therapies for RA and PsA are associated with this risk, including the risk of opportunistic infections.

The risk of serious infection has been identified as a potential concern for patients using denosumab. In the pivotal phase 3 trial for denosumab in post-menopausal women with osteoporosis, no significant difference was observed in the overall incidence of infection. However, there were a significantly higher number of serious infections, including cellulitis/erysipelas events, in denosumab-treated patients compared to placebo-treated patients.

Given that denosumab may be used concurrently with immunosuppressive biologics among patients with RA or PsA, it is important to understand the risk of serious infection in patients using these 2 therapies concurrently. There is currently limited clinical evidence on this topic.

This study was conducted to describe the occurrence of serious infections in RA or PsA patients who were concurrently treated with an immunosuppressive biologic and denosumab at 2 rheumatology clinics in the United States (US).

- **Research Question and Objectives**

Primary Objective: To describe the occurrence of serious infection in a population of patients with RA and/or PsA concurrently using an immunosuppressive biologic and denosumab.

Exploratory Objective: To describe characteristics of study patients with and without serious infection.

- **Study Design**

Retrospective cohort, chart review

- **Setting**

Two rheumatology practices located in the US: Tustin, California and Huntsville, Alabama

- **Subjects and Study Size, Including Dropouts**

The study population included RA and PsA patients treated at either of the 2 sites. Patients were administered at least 1 dose of an immunosuppressive RA or PsA biologic disease-modifying anti-rheumatic drug (DMARD) agent during the period before denosumab initiation (pre-index period) and had concurrent use of denosumab and an immunosuppressive biologic DMARD in the period after denosumab initiation (post-index period). This study included patients who were treated prior to 18 March 2015 and received care at 1 of the 2 participating clinics before and after denosumab initiation. Patients with a malignancy who were being treated with chemotherapy during the pre-index period and patients with a diagnosis of human immunodeficiency virus (HIV) infection at any time during the study period were excluded.

The final study population included 45 patients.

- **Variables and Data Sources**

Primary outcome: Serious infection defined as infection requiring hospitalization and/or intravenous (IV) antibiotics.

Secondary outcomes: Demographic and clinical characteristics, medical history, and treatment information.

The date of the first recorded administration of denosumab marked each subject's index date. The study was comprised of a pre-index period extending up to 12 months prior to the index date and a post-index period of up to 12 months. During the pre-index period, exposure was defined by use of any immunosuppressive biologic DMARD for RA or PsA. During the post-index period, exposure was defined as concurrent use of an immunosuppressive biologic DMARD and denosumab. There was no restriction on either denosumab or biologic dose and no minimum duration of concurrent exposure. Patients who switched biologics were included as long as the gap between the 2 biologics was no longer than 5 times the half-life of the prior biologic agent.

Data sources: Electronic patient charts from 2 rheumatology clinics in the US; Robin K. Dore MD, Inc and Rheumatology Associates of North Alabama.

- **Results**

Patient charts were available for a total of 45 patients who met all the study eligibility criteria. No serious infection events occurred during the period of concurrent use of denosumab and biologic DMARD. Three patients each experienced 1 serious infection event before the initiation of denosumab. All 3 patients who experienced serious infection events took non-biologic DMARDs concurrently with biologic DMARDs for RA or PsA in the pre-index period.

- **Discussion**

This study provides real world evidence on the occurrence of serious infections in RA or PsA patients who were managed with immunosuppressive biologic DMARDs and then used an immunosuppressive biologic DMARD and denosumab concurrently. However, the small sample size in this study limited the interpretation of results. Serious infection is a relatively rare event in this patient population and concomitant use of Prolia does not appear to impact this potential risk.

Conclusion

The data from this retrospective chart review study provide some real world evidence of the low incidence of serious infection associated with the concurrent use of denosumab and biologic DMARDs. The low incidence of serious infection suggests that the concomitant use of a biologic DMARD and denosumab may not pose any additional risk of serious infection beyond the risk associated with biologic DMARD use alone. However, the small sample size (N = 45), limits generalizability.

- **Marketing Authorization Holder(s)**

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