

Design and methods for a Scandinavian pharmacovigilance study of osteonecrosis of the jaw and serious infections among cancer patients treated with antiresorptive agents for the prevention of skeletal-related events

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Objective: Osteonecrosis of the jaw (ONJ) is a recognized complication of potent antiresorptive therapies, especially at the doses indicated to prevent skeletal complications for cancer patients with bone metastases. This paper describes the rationale and methods for a prospective, post-authorization safety study of cancer patients treated with antiresorptive therapies.

Methods: As part of a comprehensive pharmacovigilance plan, developed with regulators' input, the study will estimate incidence of ONJ and of serious infections among adult cancer patients with bone metastases treated with denosumab (120 mg subcutaneously) or zoledronic acid (4 mg intravenously, adjusted for renal function). Patients will be identified using routinely collected data combined with medical chart review in Denmark, Sweden, and Norway. Follow-up will extend from the first administration of antiresorptive treatment to the earliest of death, loss-to-follow-up, or 5 years after therapy initiation. Results will be reported for three treatment cohorts: denosumab-naïve patients, zoledronic acid-naïve patients, and patients who switch from bisphosphonate treatment to denosumab. ONJ cases will be identified in three newly established national ONJ databases and adjudicated by the committee that functioned during the XGEVA[®] clinical trials program.

Conclusion: This study will provide a real world counterpart to the clinical trial-estimated risks for ONJ and serious infections for cancer patients initiating denosumab or zoledronic acid. The establishment of ONJ databases in the three Scandinavian countries will have potential benefits outside this study for the elucidation of ONJ risk factors and the evaluation of ONJ treatment strategies.

Keywords: cohort study, osteonecrosis of the jaw, pharmacovigilance, postmarketing drug surveillance, denosumab, zoledronic acid

Introduction

Bone metastases and their clinical sequelae are frequent and debilitating complications for patients with advanced cancer.¹⁻⁴ Bone metastases are associated with markedly increased osteoclast activity and skeletal-related events (SREs), including pathologic fractures, radiation to bone, spinal cord compression, and surgery to bone.^{3,5,6} Until approval of the first RANK ligand (RANKL) antibody (denosumab) in 2010, intravenous (IV) bisphosphonates were the only approved treatment to prevent SREs. Denosumab is a fully human IgG₂ monoclonal antibody that inhibits RANKL, prevents

RANK activation, and thereby inhibits the formation, differentiation, and survival of osteoclasts.⁷

Efficacy results from three pivotal Phase 3 active-comparator studies of denosumab (120 mg subcutaneously [SQ] every 4 weeks [Q4W]) against the standard of care bisphosphonate (zoledronic acid, IV, 4 mg, adjusted for renal function, Q4W) established the efficacy of denosumab for the prevention of SREs.⁸⁻¹⁰ Accordingly, XGEVA[®] (denosumab 120 mg SQ Q4W) was approved in the United States (2010), Canada (2011), and the European Economic Area (2011) to prevent SREs in patients with bone metastases from solid tumors.

A serious complication observed for both treatment arms during the sponsor's clinical trial program was osteonecrosis of the jaw (ONJ). ONJ is a recognized clinical entity, defined during the clinical trial program as an area of exposed alveolar or palatal bone associated with non-healing after 8 weeks of appropriate care in a patient without a prior history of radiation therapy to the jaws.^{11,12} Since then, the American Association of Oral and Maxillofacial Surgeons' (AAOMS) definition for ONJ has broadened, as reflected in a recent position paper from AAOMS, to recognize that ONJ can manifest without exposed bone.¹³ Research suggests a strong association of ONJ with suppression of bone turnover.^{12,14,15} ONJ has been observed among 1% to 10% of cancer patients, followed for up to 36 months, treated with IV bisphosphonates for the prevention of SREs.¹⁶ In the pooled analysis of the three denosumab (120 mg SQ, Q4W) pivotal trials, at 3 years' follow-up, the proportions of subjects with ONJ were 1.8% and 1.3% among subjects who received denosumab (median time on therapy 13 months) and IV zoledronic acid (median time on therapy 12 months), respectively ($P=0.13$).¹⁷ Based on common terminology criteria for adverse events grading,¹⁸ severity was mild to moderate for all but three of the 89 ONJ cases.

As part of the marketing authorization agreement in Europe, the sponsor was required to design and implement a post-authorization safety study (PASS) of cancer patients treated with antiresorptive agents. Two endpoints were stipulated: ONJ and serious infections. The latter endpoint was included based on theoretical concerns because RANKL is expressed on activated T and B cells and in the lymph nodes, although no evidence of immunosuppression or increased risk for infection was seen in denosumab-treated cancer patients during the clinical trial program.¹⁹ The study designed to fulfill this regulatory commitment is a prospective study of Danish, Swedish, and Norwegian cancer patients with bone metastases initiating treatment with denosumab or

zoledronic acid from the first date of XGEVA[®] availability in the three countries (Denmark, September 2011; Sweden and Norway, October 2011) through the end of 2013 in Norway and Sweden, and through the end of 2014 in Denmark. The study includes three treatment cohorts: denosumab-naïve patients, zoledronic acid-naïve patients, and cancer patients who switch from bisphosphonate treatment to denosumab. The last cohort does not have a counterpart in the three pivotal clinical trials, but is of interest to European Union regulators based on the expectation that patients might switch from IV bisphosphonates to the new therapy when renal function deteriorates or when an SQ therapy is clinically preferable. Herein, we describe briefly the design and methods being employed in this study.

Methods

Cohort identification and follow-up

The Scandinavian national comprehensive health and administrative registries and databases are linkable on an individual level, within a setting of universal health care, and capture health-related data on all residents during their lifetime. A broad spectrum of health information is routinely registered, with only slight differences among the countries. Residents can be tracked in all databases from birth or immigration until death or emigration, providing virtually complete long-term follow-up. Completeness and accuracy of these records have been found to be high.^{20,21}

Eligibility criteria for this study require that patients be at least 18 years old, diagnosed with cancer, and, subsequent to the development of bone metastases, initiated antiresorptive treatment for SRE prevention with denosumab or zoledronic acid. Patients could also have switched to denosumab after receiving up to 24 treatments with oral or IV bisphosphonates at doses for cancer indications. The exclusion criteria are a history of radiation therapy to the head and neck region or having hypercalcemia of malignancy as the sole indication for (usually short-term) treatment with an antiresorptive agent.

Patients are initially identified from diagnoses (Denmark, Norway, and Sweden) and treatments (Denmark only) recorded in the national patient registries (the Danish National Patient Register,^{20,22} the Norwegian Patient Register,²³ and the National Patient Register of Sweden)²⁴ and then verified to be eligible by medical chart review. Data on vital status and dates of death or emigration are to be obtained from the population registries of the participating countries: the Danish Civil Registration System,²⁵ Statistics Norway,²⁶ and the Swedish Total Population Register.²⁷ Patients are followed annually through the relevant data systems from the first administration of antiresorptive

treatment to the earliest of death, loss-to-follow-up, or 5 years after therapy initiation, regardless of the duration of therapy. The follow-up period ends in September 2019.

The study was approved by the Danish Data Protection Agency, Danish National Board of Health, the Norwegian Regional Committee for Medical and Health Research Ethics South-East, and the Swedish Regional Ethical Review Board. The www.clinicaltrials.gov identifier is: NCT01967160.

Endpoint detection

A key challenge in registry-based PASS can be the detection of clinical outcomes with completeness and validity comparable to that of randomized trials. Therefore, as part of the development of this study, extensive validation efforts were initiated for the co-primary endpoints.

ONJ

Unlike the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) classification system used in the United States, the version of the ICD-10 classification used in the three Scandinavian countries does not have a specific code for ONJ. Accordingly, based on expert opinion, we developed an algorithm of ICD-10 codes that could conceivably be used to code ONJ. This algorithm was used to identify patients in the Danish National Patient Register during the pre-approval period 2005 through 2010 who also had a cancer diagnosis and who had sought care in Departments of Oral and Maxillofacial Surgery (DOMS) in Denmark. Then, the expert ONJ adjudication committee (ONJAC) from the sponsor's clinical trial program reviewed information abstracted from medical records for these potential cases to identify true positive cases.

Our validation efforts included 212 potential ONJ cases. Charts were available for 197 (93%) of these patients. Of these, 83 cases were adjudicated positive (positive predictive value [PPV] 42%, 95% confidence interval [CI] 35% to 49%). We also evaluated the sensitivity of the algorithm to identify known cases from a collection of ONJ cases maintained by two DOMS in Denmark. Based on 101 ONJ cases known to these two DOMS, we estimated sensitivity to be 73% (95% CI 64% to 81%). No additional ICD codes were identified that would have improved sensitivity appreciably.²⁸

The PPV and sensitivity of the ONJ algorithm were judged unsuitable to accurately estimate the incidence of ONJ for this PASS. While adjudication can solve the false positive identification problem, additional steps were necessary to address the likely under-ascertainment of cases (viz low sensitivity). Accordingly, the study team consisting of

leading oral and maxillofacial surgeons in Denmark, Sweden, and Norway established country-specific databases of ONJ cases that can be used for case identification. The process, challenges, and procedures for the establishment of these three national databases have been previously described.²⁹ Thus, ONJ case detection will involve linkage with these newly established resources for ONJ, coupled with algorithm searches of national patient databases where improvement in coding of ONJ at the DOMS level can be expected. Potential cases identified through these procedures will be adjudicated by the ONJAC so that ONJ in this PASS is defined in a manner consistent with the sponsor's clinical trials program.

Serious infection

Serious infections are common among patients with advanced cancer.³⁰ We defined a serious infection as one that was recorded in the patient registries during inpatient hospitalization. Because validity of inpatient diagnoses for infection had not been studied previously for cancer patients, we conducted such an assessment during the 5 years immediately preceding our study period.³¹

Based on an algorithm of ICD-10 codes for infection and blinded physician review of medical records for a sample of 266 patients with infection diagnoses identified from the Danish National Patient Register, the PPV of our algorithm was 98% (95% CI 96% to 99%) for any infection (the study's co-primary endpoint), supporting this approach of endpoint assessment. For specific infection subcategories that are of special interest for cancer patients, PPVs were 93% for sepsis, 84% for pneumonia, and 79% for skin infections. Sensitivity was not evaluable in this study, but clinical judgment suggests that infections leading to or associated with a hospitalization are unlikely to go unrecorded in patient databases, and that other common conditions among cancer patients are unlikely to be miscoded as infections.

Statistical analysis

The primary analytic approach chosen for this study is descriptive: to calculate cumulative year by year cohort specific incidence proportions (IPs) for the three treatment cohorts. The IP is calculated simply as the proportion of patients who manifested ONJ or a serious infection at yearly cumulative time points. In addition, incidence rates will be calculated for the cohorts after 3 and 5 years' follow-up, respectively. Incidence rates will be calculated as the number of patients who manifest ONJ or a serious infection divided by the total person-years of observation in the respective cohorts when 3 or 5 years' follow-up time has elapsed.

Comparative analyses were deemed unlikely to be valid because of the expected non-comparability of the naïve treatment cohorts to each other. In contrast to the XGEVA[®] clinical trial program where naïve patients were exchangeable at treatment assignment, exchangeability is not expected among naïve real world patients, especially for newly marketed medications.³² There is a contraindication for zoledronic acid, but not denosumab, for patients with severe or worsening renal impairment and the availability of an SQ therapy enables treatment with denosumab, but not zoledronic acid, by physicians who do not administer IV medications as part of their practices. In addition, there is also the potential for new physician adoption bias with a novel therapy like denosumab. Early adopting physicians are likely to be more comprehensive about pre-treatment oral evaluation to prevent initiation of antiresorptive therapy for patients with invasive dental treatment in the last 6 months, a strong risk factor for ONJ, and about ongoing evaluation of patients to identify oral lesions that should be referred for expert dental evaluation.³³ This could bias comparative analyses to the extent that pre-treatment evaluation and comprehensiveness of evaluation during treatment may differ for denosumab and zoledronic acid.

ONJ, by consensus definition, is only diagnosed after 8 weeks of exposed or probed alveolar or palatal bone.¹² Therefore, time at risk for ONJ will start 8 weeks after a patient receives his/her first antiresorptive treatment. Consequently, patients diagnosed with ONJ within 8 weeks of their first qualifying antiresorptive treatment will not contribute to numerators or denominators in ONJ IPs and incidence rates, and patients switching from zoledronic acid to denosumab will be at risk in the zoledronic acid cohort until 8 weeks after the switch.

There is no natural comparator for patients who switch from bisphosphonate treatment to denosumab. Switching is expected to be predominantly, though not exclusively, from zoledronic acid or other bisphosphonates to denosumab. This pattern of switching can cause some ambiguity in interpreting results for those who switch therapies to denosumab due to the long residence of bisphosphonate in the bone and the clinical experience that ONJ has been diagnosed months after bisphosphonate treatment ended.

The study was designed to include 700 to 900 patients in the denosumab-naïve cohort, all denosumab switch patients who meet eligibility criteria (expected to be at least 150), and one matched zoledronic acid patient for each denosumab patient. This study size would enable estimation of ONJ IPs with 95% CI half-widths of approximately 1% or less for the denosumab and zoledronic acid inception cohorts, and 3.7%

or less for the denosumab switch cohort. The corresponding 95% CI half-widths for serious infection IPs would be approximately 2% or less for the denosumab and zoledronic acid inception cohorts. Based on the observed 3-year cumulative incidence of ONJ during the clinical trial program and the planned 5-year follow-up in this PASS, the three treatment cohorts would be expected to yield approximately 80 to 100 cases of ONJ. These cases will be followed to ascertain ONJ severity at diagnosis and during routine clinical care, treatment practices, and the proportion of ONJ cases that resolve.

Discussion

This PASS focuses on cancer patients with bone metastases, a population characterized by relatively short survival. Based on recent studies in Denmark, 99%, 80%, and 63% of patients with bone metastases who have lung, prostate, or breast cancer, respectively, died within 2 years of their bone metastasis diagnosis date.³⁴⁻³⁶ Antiresorptive therapies effectively reduce pain and the number of debilitating SREs during patients' remaining lifespans.^{8-10,37}

Recent legislation in the United States and the European Union gave regulatory agencies the authority to require sponsors to conduct PASS as a condition of approval. The regulatory intent behind these required studies is often the assessment of rare adverse events that might surface with greater numbers of patients under observation for longer time periods than would be possible during a clinical trial program. This is especially likely for medications used to treat conditions that are not associated with high near-term mortality rates. For patients whose median life expectancy is short, such studies often focus on providing a real world estimate of the frequency of serious adverse events observed during a clinical trial program. This addresses recognized limitations of clinical trials: underrepresentation of specific patient groups and treatment in a more controlled environment than routine clinical practice.³⁸

The non-comparative analysis approach chosen in this study has as its primary utility providing a real world counterpart to the clinical trial ONJ risks for denosumab (120 mg Q4W) and zoledronic acid (4 mg Q4W). The study will also provide novel information on ONJ and serious infections for patients in routine clinical practice who switch therapies to denosumab. The fact that these treatment cohorts are likely to differ in ways that obviate comparative analyses does not reduce the value of the cohort-specific results as a measure of real world outcomes. For a condition like ONJ, which is exceedingly rare in the absence of antiresorptive therapy, the complement of a cohort-specific IP also addresses directly a question of primary interest for

practitioners and patients: viz what percent of patients can benefit from therapy without the adverse event of ONJ.

Frequently PASS may focus on adverse events that are exceedingly rare outside of patients treated with a specific class of therapeutic drug. Some of these adverse events may have low clinical awareness and be difficult to ascertain completely outside the clinical trial setting. Indeed, we established that detection of ONJ would be incomplete in the national patient registries, even with an algorithm developed to maximize sensitivity. This led to collaboration with oral and maxillofacial surgeons at centers in Denmark, Sweden, and Norway where virtually all suspected cases of ONJ are evaluated and, subsequently, to the establishment of three national databases of known ONJ cases for linkage with the treatment cohorts. Establishment of the ONJ database is therefore critical to ascertainment of ONJ risk, although the potential for underreporting of ONJ into the database remains. Potential cases identified with this approach will be adjudicated as in the denosumab clinical trial program. The establishment of these national ONJ databases will not only help to meet the requirements of the PASS for detection of ONJ, but also support broader studies of the clinical course of ONJ. Much remains to be learned about ONJ, including elucidation of risk factors that could serve as a basis for preventive activities and evaluation of treatment strategies.

Acknowledgment

This research was sponsored by Amgen Inc. The funding from Amgen Inc. received to conduct this study was issued to and administered by Aarhus University.

Disclosure

JA was formerly employed by Amgen Inc. and holds Amgen stock. VE, UHJ, and HTS are employed by the Department of Clinical Epidemiology at Aarhus University and Aarhus University Hospital. MS has consulted for Amgen Inc. as an educator and member of an expert panel on osteonecrosis. BBH has received a one-time lecture fee from Amgen Inc. CLW, AK, SEN, and SH have no conflicts of interest. HM, KÖ, and RKH are employees and stockholders of Amgen Inc.

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