Pharmacogenetics of Bisphosphonate-associated Osteonecrosis of the Jaw

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KEYWORDS

• Jaw osteonecrosis • Bisphosphonates • Pharmacogenetics • Pharmacogenomics • Genes • Single-nucleotide polymorphisms

KEY POINTS

- Osteonecrosis of the jaws (ONJ) develops in a small subgroup of individuals exposed to bisphosphonate medications.
- Although several associated clinical risk factors have been identified, it remains difficult to predict which individuals will develop ONJ.
- Pharmacogenetics has the potential to identify genetic variants associated with an increased risk (susceptibility) of developing ONJ.
- Several genome-wide association and candidate gene studies have been performed during the last few years; however, they are limited by small cohort size and lack of robust genomic statistical significance.
- The study of genetic susceptibility to ONJ requires international multicentre collaborative networks and larger and better phenotyped cohorts.

INTRODUCTION

Bisphosphonates (BPs) are antiresorptive agents commonly used in the treatment of osteoporosis, multiple myeloma, and bone metastases from solid cancers.[1] BPs are internalized into osteoclasts via endocytosis and result in the inhibition of osteoclast activity through different mechanisms.[2,3] Nitrogen-containing BPs, including alendronate, ibandronate, risedronate, pamidronate, and zoledronate, inhibit farnesyl pyrophosphate synthase, a key enzyme of the mevalonate pathway. This (1) prevents prenylation of guanosine triphosphatase (GTPase), which is essential for osteoclast function and survival, and (2) causes accumulation of isopentenyl diphosphate, which in turn can induce osteoclast apoptosis.[4] Non–nitrogen-containing BPs, including clodronate and etidronate,

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are incorporated into an adenosine triphosphate analogue, which can also induce osteoclast apoptosis.[5]

BPs are associated with a potentially severe adverse drug reaction (ADR): osteonecrosis of the jaw (ONJ), which was initially reported in 2003.[6] Since then, thousands of ONJ cases have been reported worldwide.[7] ONJ is characterized by the development of jawbone necrosis and is traditionally presented with areas of exposed necrotic jawbone through mucosal or facial skin fenestrations ranging from a few millimeters to several centimeters.[8–10] More recent studies have reported that in approximately 25% of cases ONJ can also present without soft tissue fenestration (nonexposed variant), with affected patients showing otherwise unexplained painful symptoms, intraoral or extraoral fistulae, tooth mobility or tooth loss, sinusitis, or mandibular facture.[1,11–13] Both the exposed and nonexposed variants of ONJ can present with extensive necrosis, secondary infection, and severe pain,[14] therefore causing a significant reduction in the quality of life.[15] Figures on ONJ prevalence and incidence vary widely and remain controversial. Available data suggest that ONJ develops in a subgroup of individuals who use or have used BPs: approximately 7% among those using intravenous BPs for cancer management and 0.12% of those who take oral BPs because of osteoporosis.[16] Little robust information is available regarding ONJ etiopathogenesis; similarly, it is unclear why ONJ develops only in a subset of patients.[17,18] Several clinical risk factors have been associated with ONJ development, including underlying malignant disease, use of intravenous high-potency BPs, high-dose or long-term BP therapy, use of concomitant medications, dental infections, and surgical procedures to the jawbones.[19] Nevertheless, relevant literature lacks robustness and consistency, and in most instances ONJ remains an unpredictable ADR.

Interindividual genetic variants are known to potentially determine disparate response to medications, including toxicity. It was estimated that genetic variability could contribute to ADR development in more than half of the medications examined in a systematic review.[20] Interindividual genetic variability can therefore contribute to explaining ONJ development in a subset of individuals using BPs. In the past few years, several small studies have investigated the potential association of ONJ development with genetic factors.[21–31] This article provides a critical and comprehensive review of the available evidence regarding pharmacogenetics of ONJ.

PHARMACOGENETICS AND ADVERSE DRUG REACTIONS

Pharmacogenetics is the study of how genetic differences influence the variability in patients' responses to drugs, including toxicity.[32] Examples of genetic factors contributing to individuals' susceptibility to ADR include *HLA-A*31:01* for carbamazepine (CMZ)-induced skin reactions in Europeans,[33] *HLA-B*15:02* for CMZ-induced Stevens-Johnson syndrome in Asians,[34] *SLCO1B1* for statin-induced myopathy,[35] and *HLA-B*57:01* for abacavir-induced hypersensitivity reactions,[36,37] as well as for flucloxacillin-induced liver injury.[38] In most cases, the genetic risk variants are drug specific (1 or a few medications) and population (ethnicity) specific.[33,34,39] Among the drug-induced liver injuries, *HLA-B*57:01* is only known to be associated with flucloxacillin-induced reactions, although *HLA-DRB1*15:01* is known to be associated with both amoxicillin-clavulanate[39] and lumiracoxib.[40] Examples of successful and cost-effective translation of pharmacogenetic data into clinical practice include *HLA-B*57:01* screening before initiating treatment with abacavir and *HLA-B*15:02* screening before CMZ therapy in Asians, both recommended by the US Food and Drug Administration.[41,42] With such robust and growing evidence, pharmacogenetics is becoming a realistic mean to tailor and personalize safe and effective therapy for single individuals.[43] Pharmacogenetic studies comprise genome-wide association studies (GWASs) and candidate gene studies.[44] A total of 2 GWASs and 9 candidate gene studies have been performed in relation to ONJ.

GENOME-WIDE ASSOCIATION STUDIES ON OSTEONECROSIS OF THE JAW

GWAS is a comprehensive research approach that is useful for investigating both complex disease and drug response, including ADR. Typically, a GWAS screens millions of single-nucleotide polymorphisms (SNPs) across the entire genome, in which an SNP refers to a single-base difference in DNA sequence present in at least 1% of the general population.[45] The large set of SNPs, which form part of a standard GWAS genotyping chip, have been chosen based on their property of being proxies to others within the same genomic region; this is known as linkage disequilibrium (LD).[32] A successful GWAS relies on a reasonably complete coverage of genetic variants, which include SNPs that are typed with a chip, as well as SNPs that have not been typed but can be predicted through LD; a causal variant can be a typed SNP, or an