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総　　説

# 臨床試験デザイン

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# Clinical Trial Design

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## 抄　　録

臨床試験はデザイン・計画の段階から始まり，試験実施・データ管理・モニタリングを経て，データ解析・報告書作成に至る．この各ステップが統計的方法を必要としている．再現性によって結果を保証することが可能な基礎実験と異なり，同じデザインで繰り返すことが困難な臨床試験においては，デザインと手続きの妥当性から結果を保証するしかない．計画段階から生物統計学の専門家が参画していれば，質の高い臨床試験を実施できる可能性は高い．近年，臨床試験にベイズ流の方法が有用であるという報告は着実に増えている．効率的かつ倫理的な試験デザインの開発は，資源を有効に活用するという観点から今後ますます重要になるであろう．本稿では，ランダム化対照試験の標準的方法，および探索的臨床試験のデザインとして有用であるベイズ流の方法について述べる．

**キーワード**：技術評価，統計的仮説，ランダム化，統計的考察，ベイズ流統計学．

## Abstract

Every clinical trial starts from the design and planning stage, moves to trial conduct, data management and monitoring, and finally to the data analysis and conclusions. Each step along the way calls for statistical methods. While basic research which can be guaranteed a result by reproducibility, clinical trials which cannot be repeated with the same design must be guaranteed by the validity of design and procedure. If a biostatistician take part in the planning stage, we can do the high quality of clinical trials. In recent years, reports insisting on the usefulness of Bayesian statistics in clinical studies have steadily increased. The development of efficient and ethical design will become important in the future, from the viewpoint of the best use of resources. In this paper, I will describe the standard methods for randomized clinical trials, and Bayesian methods which could be useful for the design of exploratory clinical trials.

**Key Words**: Technology assessment, Statistical hypothesis, Randomization, Statistical consideration, Bayesian statistics.

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## はじめに

臨床試験はデザイン・計画の段階から始まり，試験実施・データ管理・モニタリングを経て，データ解析・報告書作成に至る．この各ステップが統計的方法を必要としている．臨床試験は，良いデザインおよび正しい遂行がなければ，台無し（例えば，結論の出ないまたは誤った知見を導く）になり，さらには大惨事（例えば，不必要に多数の患者が毒性または死を被ることを引き起こす）になる可能性さえある．臨床試験は効率的かつ倫理的であるべきで，資源を節約し，より多くの患者に恩恵を与え，より迅速に正しい結論を引き出し，結果として不必要な毒性をより少なくすべきである[1]．本稿では，ランダム化対照試験の標準的方法，および探索的臨床試験のデザインとして有用であるベイズ流（Bayesian）の方法について述べる．

## 医学・医療と技術評価

医学は普遍性のある真実を追求する科学の一分野である一方，医療は多様性のある個人に対して最適な技術を選択して適用することが要求される場である．技術評価は，主に統計学に基づく科学的方法を駆使して医療技術を相対的に評価し，医学から医療への橋渡しを行う（図1）．

統計学を医学・医療の領域に導入する際には，2つの大きなギャップを認識しておく必要がある．1つは，「決定論」と「非決定論（確率論）」のギャップである．1800年代半ばにクロード・ベルナールが「統計学に立脚している限り，医学は永久に推測科学に止まるであろう」と決定論的な考え方を主張して以来，医学の世界では決定論的な思想が支配的である．もう1つのギャップは，意思決定の主体に関わる問題であり，「対集団の確率」と「対個人の確率」とのギャップである．たとえば，ある医薬品を承認すべきかどうかという判断は，その国の人々という集団に対するベネフィットとリスクのバランスで決定される．その決定は「対集団の確率」に基づく一方，医療の場で診断や治療を行う際には，個人に対するベネフィットとリスクを評価しなければならない．たとえば，胎児診断を行って，医師が「胎児に異常がある確率は80%」と言ったとき，その80%は集団での頻度に基づいたものである．しかしながら，それを聞いた母親の「子供には異常があるか（100%），ないか（0%）のどちらか」という感覚で，この確率を解釈することはそれほど容易ではない．これは「確率とは何か」という哲学的課題につながっている．

臨床試験は，20世紀を代表する英国の統計学

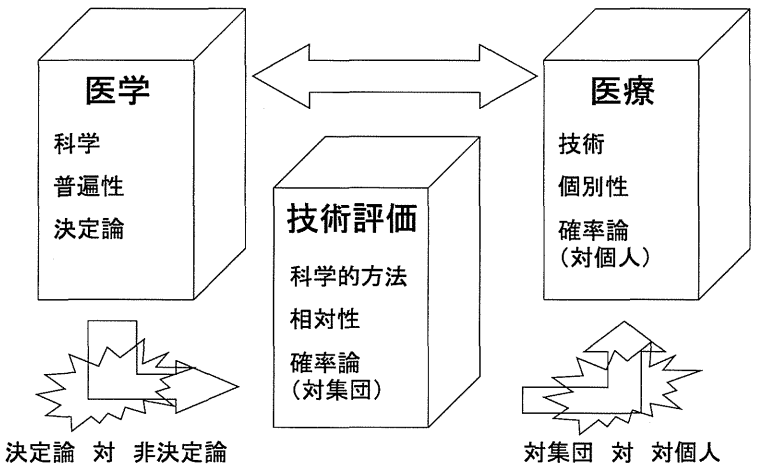


図1 医学・医療と技術評価

者 R.A. フィッシャー（1890～1962）が創始した統計的実験（技術的実験とも呼ばれる）の方法論を基礎としている．科学的実験は，人工的に作り出された純粋な条件のもとでの因果関係を確定しようとするのに対して，統計的実験は以下の特徴を有する[2]．

・実験の場は，現実の応用の場に近い状況に設定される
・結果の分析には誤差の存在を前提にしなければならない
・いくつかの因子を同時に変化させて結果を見る必要があることがある
・目的は，何らかの基準によって現実の場において最も良い結果が得られるような条件を求めることである

様々な種類の誤差を伴うデータを扱うためには統計的方法が不可欠である．また，再現性によって結果を保証することが可能な基礎研究と異なり，同じデザインで繰り返すことが困難な臨床試験においては，デザインと手続きの妥当性から結果を保証するしかない．

### 探索的試験と検証的試験

臨床試験の性格は検証的試験と探索的試験に大別される．検証的試験は有効性または安全性の確固たる証拠を提示するための試験と位置付けられる．ただし，個々のいかなる試験も検証的側面と探索的側面の両方を持つ．試験実施計画書（以下，プロトコル）には，各試験について検証的な証明として用いられる側面と，探索的解析のためにデータを提供する側面とを，明確に区別しておくべきである[3]．探索的解析から得られた結果は仮説に過ぎず，その仮説は検証的試験によって確認しなければならない．

## 統計的仮説

統計的仮説の代表的なものは，優越性仮説と非劣性仮説である．優越性仮説を証明しようとする試験（優越性試験）とは，試験治療の効果が対照治療（活性対照またはプラセボ対照）よりも「臨床的に優れること」を示すことが目的の試験である．一方，非劣性仮説を証明しようとする試験（非劣性試験）とは，試験治療の効果が対照治療よりも「臨床的に劣らないこと」を示すことが目的の試験である．多くの場合は優越性仮説が設定されるが，対照治療（通常，活性対照）に比べて安全性あるいは経済性に優れていることが見込まれる場合に，このような非劣性仮説が許容されることがある．

非劣性試験を計画する際には，非劣性マージン（臨床的に意味のある最小の差：Δ）の決定，データの質などについて十分な注意が必要である．ハザード比を治療効果の尺度とした臨床試験の場合，優越性試験では，ハザード比の 95% 信頼区間の上限が 1 より小さければ，有意水準 5% で試験治療が優れると判断される．一方，非劣性試験では，その 95% 信頼区間の上限が $1+\Delta$ よりも小さければ，有意水準 5% で試験治療は対照治療に $\Delta$ 以上は劣らない，と判断される（図 2）．

## ランダム化

ランダム化対照試験では，登録の際にランダム化という操作が必要になる（図 3）．ランダム化を行うことにより，試験群と対照群の比較可能性（内的妥当性とも呼ばれる）が保証される．ランダム化は「実験計画法」を確立したフィッシャーの偉大な発明の一つである．実験に伴う誤差には以下の 2 種類がある．ちなみに，フィッシャーは臨床試験ではなく，農事実験に従事していた．

・偶然誤差…測定誤差のようにある確率分布に従うと想定できる誤差であり，繰り返し測定を行えばその大きさについて推定可能である
・系統誤差またはバイアス…圃場の肥沃度や日当たりの不均一性のように確率変動と見なせない誤差であり，繰り返しには関係なく結果を歪める原因となる

ランダム化の目的は，一言で言うと「系統誤差を偶然誤差に転化すること」である．臨床試験におけるその意義は，

・予後因子が既知か未知かにかかわらず，予後因子の分布が類似したグループを作る

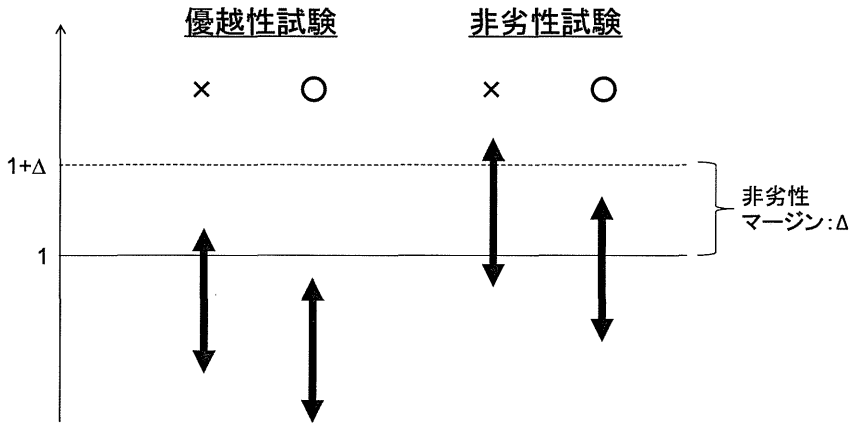


図2 優越性試験と非劣性試験の判断規準

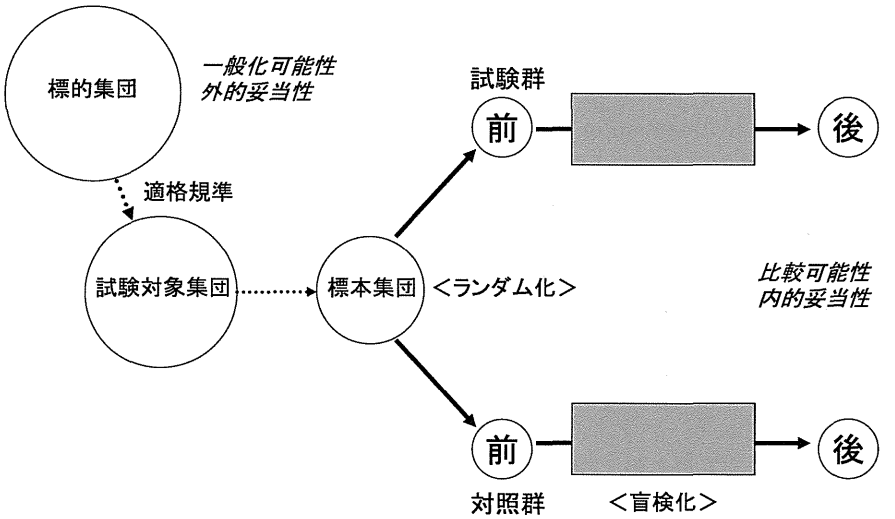


図3 ランダム化対照試験

・データ解析の際に治療効果の定量的な評価のための正しい統計的根拠を与えることである[3].

臨床試験で利用されるランダム化の方法は，固定的割付（単純ランダム化，並べ替えブロックランダム化など）と適応的割付（偏コインデザイン，最小化法など）とに分類される．重要な予後因子の分布を治療群間で均等にするためには，それらの因子で層を作り，その層ごとにランダム化（層別ランダム化）を行う必要がある．ランダム化の方法には多くの選択肢があり，試験統計家がそれぞれの利点と欠点を考慮して決定すべきである．

## 統 計 的 考 察

試験統計家がプロトコルに記載すべき統計的事項として，「標本サイズの設定根拠」，「解析対象集団」，「解析項目・方法」，「中間モニタリン

グ」がある．

**1．標本サイズの設定根拠**

臨床試験に参加していただく対象数（標本サイズ）は科学性，倫理性，実施可能性のバランスを考慮して決める必要があり，多すぎても少なすぎてもいけない．標本サイズは主要評価項目に関する情報に基づいて計算される．その時点における情報を最大限利用するものの，一時的な仮定に基づく概算であることに注意が必要である．例えば，ある癌の補助化学療法の臨床試験において，標準治療を受ける患者の5年生存率を予測する場合，利用できる情報にはかなり大きなばらつきがある．これらの前提条件を慎重に検討した上で，通常は仮説検定に基づく決定方式に従って，帰無仮説，対立仮説，検定統計量，有意水準，第Ⅰ種の過誤，第Ⅱ種の過誤または検出力などが試験の性格（探索的または検証的）を考慮して決定される．

**2．解析対象集団**

解析対象集団は，ITT（intention-to-treat）の原則に従って定義すべきである．これは，「被験者が実際に受けた治療ではなく，被験者を治療しようとした意図（intention to treat）に基づいて評価する」という原則である[3]．従って，登録されたすべての被験者を解析対象とすることが原則であるが，登録後に判明した不適格例，試験治療を全く受けなかった例を対象から除くことは一般的に許容される．いずれにしても，有効性および安全性に関する主要な解析対象集団の定義をプロトコルに明記し，報告時には解析対象から除外した対象数とその理由を明記する必要がある．

全体集団のある一部のグループを対象とした解析をサブグループ解析（サブセット解析，部分集団解析）と呼ぶ．通常，患者特性やベースライン情報に基づいてサブグループ化を行う．「試験治療を完遂した集団」のように介入後の情報に基づいて対象を選択する場合には，比較可能性など別の問題が生じるため，サブグループ解析とは区別しておく必要がある．ランダム化の際に層別に用いた因子によるサブグループ解析は，ランダム化に基づく比較可能性の条件を満たしている．そうでない場合は比較可能性の条件を満たさない．ただ，その条件を無視したとしても，多数の検定の実施により第1種の過誤確率が上昇すること，一方ではサブグループ内の標本サイズ不足により検出力が低下することが問題となる．対応策としては，1）関心のある少数のサブグループを事前にプロトコルに記載する，および2）交互作用の検定が有意な場合にのみサブグループでの検定を行うことが推奨されている．交互作用には，量的交互作用と質的交互作用の2種類があり，交互作用が検出されたときは有意差の有無だけでなく，医学的な意義と解釈について十分な吟味が必要である．いずれにしても，サブグループ解析は，探索的解析の代表的なものであり，その目的は仮説の生成である．

**3．解析項目・方法**

臨床試験で利用される標準的な統計解析手法について表1に示す．ランダム化対照試験では，ランダム化によって比較可能性が保証されているので，通常は観察研究のように複雑な回帰モデルを用いて交絡因子を調整する必要はない．

**4．中間モニタリング**

中間モニタリング（中間解析，中間評価とも呼ばれる）の目的は，

- 試験治療の優越性が疑いなく立証された場合
- 適切な試験治療の差を示す見込みがないことが判明した場合
- 許容できない有害事象が明らかになった場合

に試験を早期に中止することである[3]．検定の多重性を考慮した中止規則の設定には多くの方法（グループ逐次法など）が開発されてきているが，実際に臨床試験を中止すべきかどうかという判断は純粋に統計的な問題ではなく，臨床的のみならず社会的な影響も考慮する必要がある．そのような判断を公正に行う場として，中間モニタリングを実施する際には，当該臨床試験に関与しない第三者からなるデータモニタリング委員会（効果安全性評価委員会とも呼ばれ

表1 変数の型別の標準的な統計解析手法

| 目的 | 連続変数 | 分類変数 | 時間-イベント変数 |
|---|---|---|---|
| 分布の記述 | ヒストグラム、箱ヒゲ図、散布図 | ヒストグラム、分割表 | 生存曲線（Kaplan-Meier法） |
| 要約統計量 | 平均、分散、中央値、パーセント点、相関係数 | 頻度、一致度、相関係数 | x年生存率、中央生存期間 |
| 検定（単純） | t検定、分散分析、Wilcoxon検定 | $\chi^2$検定、Fisher正確検定 | ログランク検定 |
| 検定（層別） | 共分散分析 | Mantel-Haenszel検定 | 層別ログランク検定 |
| 回帰モデル | 重回帰分析 | ロジスティック回帰分析 | Cox回帰分析 |

る）を設置しなければならない.

## 探索的臨床試験のデザイン —ベイズ流の方法

1950年頃に臨床試験の方法論がほぼ確立して以来，統計的評価の方法として，フィッシャーあるいはネイマン・ピアソンによる頻度流（frequentist）の仮説検定・推定が主に用いられてきた．データ解析へのベイズ流統計学の適用は，物理学をはじめとする多くの自然科学分野および社会科学分野で広く行われており，医学・生物学分野においても，ベイズ流の統計モデルを適用したデータ解析の事例は多く存在する．しかしながら，臨床試験のデザインにベイズ流の方法を適用した事例としては，抗がん剤の第Ⅰ相試験（最大耐用量を決定するための試験）でのCRM（continual reassessment method），ランダム化試験の中間解析でのベイズ流予測確率の利用などがあるが，未だそれほど多くない.

大学等の研究機関が主体となって実施するトランスレーショナルリサーチおよび臨床試験の対象疾患は，難治性かつ重篤であり，そのうえ患者数が限られているという特徴がある．このような状況では，基礎研究で認められたコンセプトを実証するためのPOC（proof of concept）試験と呼ばれる探索的試験の実施が主であり，疾患の重篤性などを考えると同時対照を設定すること自体困難な場合が多い．また，被験者のリスクを最小にするために臨床試験の途中で結果をモニタリングしながら意思決定を行うというような柔軟な対応も必要である．さらに，被験者数を最小にするために，過去に得られた証拠や情報（事前情報）を十分に生かすことも重要となる．これらを鑑みると，予期しない事態が発生して試験途中でデザイン（標本サイズや中間モニタリングの時期・方法など）の変更を行う場合などに，頻度流接近法に基づく方法は柔軟性の観点から不十分であり，新しい方法の開発が必要となる．近年，ベイズ流接近法は柔軟性と効率性の面から有望と考えられている．臨床試験におけるベイズ流接近法の主な特長は以下の通りである.

① 解釈が容易な「確率」だけを用いて整合性のある推測と意思決定を行うことができる
② 標本サイズに関わらず事前分布を事後分布に更新して推測ができる
③ 予測分布を用いて試験結果を予測することができる

また，ベイズ流デザインの動作特性が頻度流に評価できることも1つの利点である.

## ベイズ流デザインの例

すべての被験者に同一の試験治療を行う単群臨床試験は，探索的な臨床試験の大部分を占めている．その主目的は，治療効果に対する確定的な証拠を得ることではなく，さらに研究を継続すべき有望な治療をスクリーニングすることである．単群臨床試験デザインの多くは，効果が認められない場合は試験を早期中止することが望ましい致死的な疾患の領域で開発されてきた．抗がん剤の第Ⅱ相単群臨床試験については，1960年代から頻度流の方法が開発され，1990年代以降ベイズ流接近法を用いたデザインがいくつか提案されている．その中には，効用／損失関数を明示的に用いるベイズ流決定理論に基づく手法も含まれる．

ここで，被験者20名にある試験治療を行い，14名に「効果あり（成功）」，6名に「効果なし（失敗）」という結果が得られた，二値（成功または失敗）評価項目の単群臨床試験という単純な事例を用いてベイズ流の方法を概説する．まず，事前情報が存在しないと仮定し，事前分布を一様分布（Beta(1,1)と表現されるベータ分布）と定める．次に，ベイズの定理を用いて，事前分布と観察データ（実際には尤度［ゆうど］と呼ばれる形に変換されたもの）を結合し，事後分布Beta(15,7)（＝Beta (1＋14, 1＋6)）を得る（図4）．このように更新された事後分布から，この治療の成功確率の平均は0.68(＝15/(15＋7))，成功確率が0.5以下の確率は分布下面積から0.039と得られる．この結果から，引き続いて5名の被験者に同じ治療を行ったときに何名の被験者に成功が観察されるかという予測分布を得ることもできる（図5）．

## お　わ　り　に

フィッシャーは1938年に次のように述べている；「同じだけの時間と労力をかけたとしてもデータ収集の過程，または実験計画を厳密に検討しているか否かによって，得られる収穫は10倍から12倍にもなる．実験終了後に統計学者に相談を持ちかけるのは，統計学者に，単に死後診察を行って下さいと頼むようなものである．統計学者はおそらく何が原因で実験が失敗したかという実験の死因について意見を述べてくれるだけであろう」[4]．

臨床試験に統計的方法は必須であり，計画段階から生物統計学の専門家が参画していれば，

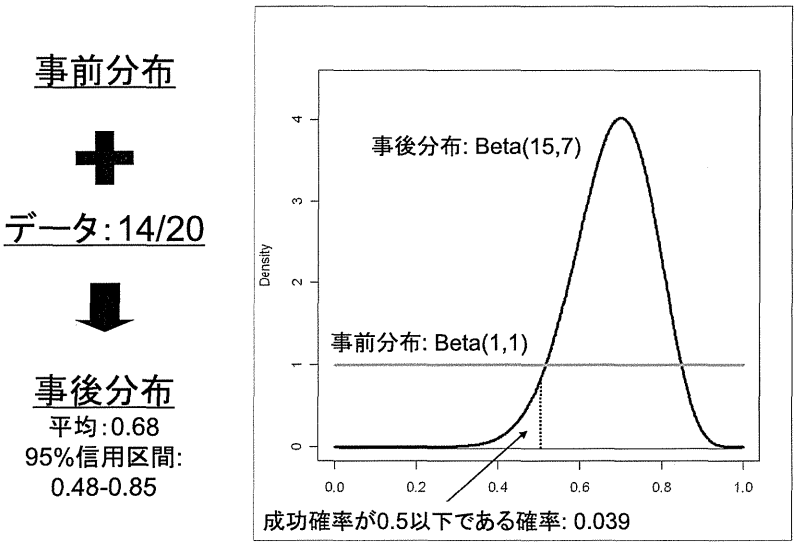


図4　事前分布から事後分布へ

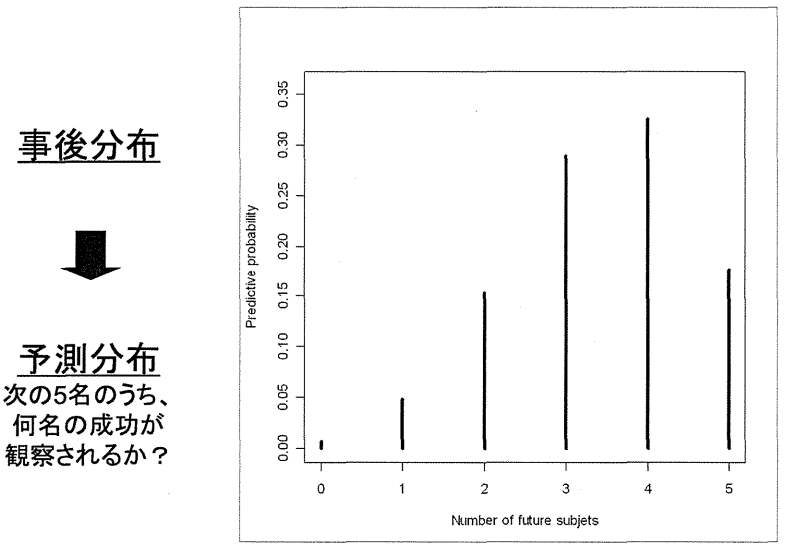


図5 事後分布から予測分布へ

質の高い臨床試験を実施できる可能性は高い．近年，臨床試験にベイズ流の方法が有用であるという報告は着実に増えている．効率的かつ倫理的な試験デザインの開発は，資源を有効に活用するという観点からも今後ますます重要になるであろう．

開示すべき潜在的利益相反状態はない．

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ORIGINAL REPORT

# The increase in prescriptions of bisphosphonates and the incidence proportion of osteonecrosis of the jaw after risk communication activities in Japan: a hospital-based cohort study†

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## ABSTRACT

**Purpose** The purpose of this study was to investigate the impact of risk communication about bisphosphonate (BP)-related osteonecrosis of the jaw (ONJ) on the number of reported cases to the Drug Adverse Reactions Reporting System and on the incidence proportion of ONJ in a hospital-based cohort study in Japan.

**Method** We conducted a survey of the safety information on BP-related ONJ available from regulatory authorities, pharmaceutical manufacturers and academic associations. We also performed a trend analysis of a dataset from the Drug Adverse Reactions Reporting System and a sub-analysis, using previously constructed data from a retrospective cohort study.

**Results** Risk communication from pharmaceutical manufacturers and academic associations began within 1 year after revisions were made to the package inserts, in October 2006. Twenty times more cases of ONJ have been reported to regulatory authority since 2007, compared with the period before 2007. In our cohort, the incidence proportion of ONJ during and after 2009 was four times greater than before 2009. During this period, BPs were frequently prescribed, whereas there was no increase in the use of alternative agents, such as selective estrogen receptor modulators.

**Conclusion** ONJ was increasingly diagnosed after risk communication efforts, but the impact of the communications was not clear. Safety notifications were diligently disseminated after the package insert was revised. However, there was no surveillance for ONJ before the revision. © 2014 The Authors. *Pharmacoepidemiology and Drug Safety* published by John Wiley & Sons, Ltd.

KEY WORDS—risk communication; osteonecrosis of the jaw; oral bisphosphonates; pharmacoepidemiology

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## INTRODUCTION

Osteonecrosis of the jaw (ONJ), also called osteomyelitis of the jaw, is defined as the presence of exposed bone in the maxillofacial region that does not heal within 8 weeks.[1–3] ONJ has received increasing attention since case reports about patients exposed to bisphosphonates (BPs) were published in 2003.[4,5] In the United States of America (USA), regulatory authorities first indicated safety concerns about zoledronic acid and pamidronate with regard to osteonecrosis in 2003.[6] In 2004, the manufacturer of zoledronic acid revised the package insert in the USA and issued a "Dear Health Professional" letter.[7] Safety notifications regarding osteonecrosis were issued in other regions, such as Canada, Australia, New Zealand[7]

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and Japan, in 2004 and 2005. Early case reports were followed by the publication of epidemiological studies in 2005 and 2006.[8–10] Thereafter, position papers,[11] guidelines[12] and expert panel recommendations[3,13] were published in 2006 and 2007. Some of these papers cautioned patients receiving oral BPs.[3,11,13] The risk of ONJ for patients receiving oral BPs was considered much lower than the risk for patients receiving intravenous BPs.[11,13] However, the incidence proportion of an adverse reaction was not fully studied until later, when the risk associated with oral BPs was proved to be smaller than that for intravenous BPs.[14,15]

Although dissemination of safety information to health care professionals or patients is the most common method for minimizing risk when a novel safety concern is discovered, the impact of risk communication has remained unknown and cannot be guaranteed to result in the intended effect.[16,17] Few studies have addressed the long-term impact of risk communication on the incidence of adverse events and whether adverse events have been successfully reduced. Instead, the impact of risk communication is often assessed by measuring processes such as changes in drug use and by laboratory monitoring.[17] Because ONJ is uncommon in the general population and its background incidence rate is low, we attributed an increase in disease reports to greater recognition of the disease among BP-exposed patients after risk communication, if the characteristics of the patients and the use of BPs did not change substantially. We expected that the risk communication initiative would decrease the incidence proportion of ONJ among BP-exposed patients, after a temporary increase.

The purpose of this study was to investigate the impact of risk communication on oral BP-related ONJ in Japan; on the number of reported cases to the Japanese regulatory authority, the Drug Adverse Reactions Reporting System of the Pharmaceuticals and Medical Devices Agency (PMDA); and on the incidence proportion of ONJ in a hospital-based cohort study of 6923 osteoporosis patients at Kyoto University Hospital.

## METHODS

We surveyed safety information about oral BP-related ONJ that was produced by the PMDA, pharmaceutical manufacturers and academic associations. We also conducted a trend analysis of a dataset from the Drug Adverse Reactions Reporting System of the PMDA and a sub-analysis, using the previously constructed data from a retrospective cohort study that was conducted at Kyoto University Hospital from February 2011 to July 2012.[18] The protocol was approved by the Ethical Committee of the Graduate School of Medicine, Kyoto University (E1445).

### *Risk communication regarding oral BP-related ONJ*

First, we surveyed the safety information from the PMDA by searching the PMDA Web site for the words "jaw" or "BPs" (accessed June to July 2012). We extracted articles on periodic safety information and letters and guidance publications, and we listed the relevant information after removing duplicate information. Second, we surveyed the types of risk communication materials concerning oral BP-related ONJ that were released by manufacturers marketing oral BPs in Japan and how and when they were disseminated. Two pharmaceutical companies collected letters and guidelines from the 10 manufacturers marketing oral BPs in Japan between July 2012 and January 2013. Finally, we collected information on the risk communications materials (type, timing of dissemination and method of dissemination) that were released by two academic associations (the Japanese Society of Oral and Maxillofacial Surgeons and the Japanese Society for Bone and Mineral Research) between July and August 2012. One of the authors, a medical doctor, reviewed the collected communications materials and summarized the warnings and recommendations announced in the communications.

### *Reported cases of ONJ to the regulatory authority*

A dataset containing the adverse drug reactions reported to the Drug Adverse Reactions Reporting System of the PMDA between April 2004 and December 2011 was downloaded, and the cases of ONJ suspected to be adverse reactions to osteoporosis medications (including oral BPs) were counted. We used the preferred terms in the Standardized Medical Dictionary for Regulatory Activities (MedDRA) Queries for "osteonecrosis," with the exception of anatomically irrelevant terms, to retrieve the cases of ONJ. The list of drugs included in this study is shown in Appendix 1.

### *Cohort study*

We conducted a cohort study of outpatients and inpatients who were diagnosed with osteoporosis, using the International Classification of Diseases (ICD-10) code (Appendix 2), and who received at least one prescription for an osteoporosis medication at Kyoto University Hospital during a study period (November 2000 to October 2010).[18] The exclusion criteria were as follows: age younger than 20 years old; primary or

metastatic tumors in the maxillofacial region; history of trauma or radiation therapy in the maxillofacial region; and intravenous treatment with BPs.

We extracted the clinical data from the electronic medical records (EMRs) using an EMR retrieval system.[19] This system retrieves electronic data for outpatients and inpatients at Kyoto University Hospital, including demographic data, diagnoses and ICD-10 codes, medications and injections, laboratory tests and radiological and pathological studies. The median duration of oral BP administration, co-medications and comorbid conditions were also extracted using the EMR retrieval system.

The medications administered for osteoporosis between November 2000 and October 2010 in this cohort were collected by the retrieval system. The list of drugs included in the cohort study is shown in Appendix 3. The numbers of BP users, estrogen users and other osteoporosis drug(s) users in the cohort were calculated for each year, counting patients who were prescribed medications at least once during that year, regardless of the use of other osteoporosis medications.

To identify relevant ONJ cases, we reviewed the radiographic imaging and clinical records of the patients with a diagnosis of not only ONJ but also inflammatory conditions of the jaw that were possibly related to ONJ, as specified by the ICD-10 codes (Appendix 4). The diagnostic criteria were detailed in a previous report.[18] Briefly, ONJ was diagnosed independently by two oral and maxillofacial surgeons in accordance with the proposed criteria, using the findings from panoramic X-rays, technetium bone scans, computed tomography, histological images or surgery. We grouped the cases of osteomyelitis of the jaw with ONJ because we considered it difficult to distinguish between these two diseases. The radiographic findings for jawbone infections in patients treated with BPs are similar to those for ONJ related to BPs,[20–22] and the presence of osteonecrosis is a common histopathologic finding, both in ONJ and in osteomyelitis of the jaw related to BPs.[23]

The incidence proportion of confirmed ONJ was defined as the number of manually confirmed, newly developed ONJ cases in the cohort (e.g., BP group or non-BP group) in 2000–2002, 2003–2004, 2005–2006, 2007–2008 and 2009–2010, divided by the size of the cohort for each 2- or 3-year period. The BP group included the patients who were prescribed BPs at least once during the period and/or in the past, regardless of the use of other osteoporosis medications; the non-BP group included the patients who were prescribed osteoporosis medication(s) other than BPs and those who had never been prescribed BPs.

The distinction between BP users in the drug use survey and the BP group in the incidence proportion survey was as follows: we classified a patient who received both BPs and estrogen in the same year as one BP user and one estrogen user over the same time period in the drug use survey. However, we classified the patient into the BP group rather than the non-BP group in the incidence proportion survey. This distinction was made because the impact of osteoporosis medications other than BPs on the incidence proportion of ONJ was considered to be negligible.

We evaluated the proportions of the cases recorded as inflammatory conditions of the jaw and alveolitis of the jaw (specified by ICD-10 codes K10.2, K10.3 and K10.0 [Appendix 4] in the EMR); the proportions were defined as the number of newly recorded cases of the inflammatory condition of the jaw in the EMRs of the cohort (e.g., BP users or non-BP users) during each 2- or 3-year period, divided by the size of the cohort during the period.

## RESULTS

### *Risk communication regarding oral BP-related ONJ*

The risk communication materials regarding oral BP-related ONJ, released by the PMDA, pharmaceutical manufacturers and academic associations, are listed in Table 1. The pharmaceutical manufacturers revised the package inserts in October 2006. The case reports or epidemiological studies regarding ONJ were published after the package insert was revised. Six separate but overlapping guidance announcements, in addition to the package insert, were issued. An academic association held educational meetings for health professionals and patients during their annual meeting in April 2008.

### *Reported cases of ONJ to the regulatory authority*

An increasing number of cases of ONJ that were suspected adverse reactions to oral BPs were reported to the PMDA after 2007, immediately after the safety information was disseminated (Figure 1). These cases included those with a past history of ONJ (that is, cases of ONJ that occurred earlier were reported as cases of ONJ after 2004 in the system). There were nearly 20 times more reported cases of ONJ during and after 2007, compared with the number of cases during and before 2006. Reported cases of ONJ that are suspected to have been adverse reactions to osteoporosis medications other than BPs have been rare. For reference, the estimated numbers of patients taking oral BPs in Japan were 2 082 928 in 2007 and 2 470 979 in 2008.[24]

### *Cohort study*

The cohort consisted of 6923 osteoporosis patients; 4129 were prescribed oral BPs (59.6%; mean age,

Table 1. Risk communication about oral BP-related ONJ in Japan

| Date* | Organization | Content |
|---|---|---|
| Oct. 2006 | PMDA†, pharmaceutical manufacturers | Measure: revised package insert for alendronate and risedronate<br>"ONJ has been reported in patients receiving bisphosphonates. The majority of reported cases have been associated with dental procedures, such as tooth extraction, or with local infection. Physicians should fully disclose the adverse reactions to their patients and observe them closely." |
| Jan. 2007 | pharmaceutical manufacturers | Notices to hospitals and "Dear Health Professional" letters to inform them about the content of the revised package insert |
| June 2007 | academic association | Publication of a case report[33]<br>There was one case of osteoporosis diagnosed with oral BP-related ONJ; the other case, a case of multiple myeloma, was diagnosed with iv BP-related ONJ. |
| Sep. 2007 | PMDA, pharmaceutical manufacturers | Measure: revised package insert for etidronate |
| Oct. 2007 | academic association | Publication of an observational study[34]<br>Questionnaires were sent to 239 institutions, and 30 patients with osteonecrosis were reported. Of them, 20 patients received iv BPs, eight received oral BPs and one received both. |
| Jan. 2008 | academic association | News article entitled "osteonecrosis of the jaws induced by anti-osteoporosis treatment"<br>"Patients on BP therapy requiring dental procedures should tell their dentists that they are being treated with BPs, and physicians should fully explain the adverse reactions to their patients when prescribing BPs." |
| Jan. 2008 | academic association, pharmaceutical manufacturers | Announcement of a guidance publication, entitled "Bisphosphonates and osteonecrosis of the jaw"<br>A 20-page pamphlet, with the diagnostic criteria, clinical manifestations, risk factors and epidemiology of iv and oral BP-related osteonecrosis of the jaw and instructions for physicians, pharmacists, dentists and oral surgeons |
| Mar. 2008 | academic association | Announcement of guidance publication, entitled "management of patients on BP therapy"<br>A four-page pamphlet with the diagnostic criteria, management, risk factors, epidemiology of iv and oral BP-related osteonecrosis of the jaw and instructions for physicians, dentists and oral surgeons |
| Apr. 2008 | academic association | Public meeting for citizens: "The state of osteonecrosis of the jaw related to BPs" |
| Sep. 2008 | academic association | A pamphlet, entitled "Bisphosphonates and osteonecrosis of the jaw: clinical manifestations and guidelines for management, 2008" |
| Feb. 2009 | academic association | Training session for dentists, entitled "The state of osteonecrosis of the jaw related to BPs" |
| Feb. 2009 | academic association | News article, entitled "Bisphosphonates and osteonecrosis of the jaws" |
| May 2009 | PMDA, academic association | Announcement of a guidance publication, entitled "Bisphosphonate-Related Osteonecrosis of the Jaws"[35]<br>This official therapeutic manual for severe adverse reactions included the diagnostic criteria, clinical manifestations, risk factors and management methods for iv and oral BP-related osteonecrosis of the jaw for citizens and health care professionals |
| June 2009 | academic association | Public meeting for citizens, entitled "The state and the management of osteonecrosis of the jaws related to BPs" |
| July 2009 | academic association | Training meeting regarding BP-related osteonecrosis of the jaw for health care professionals |
| Nov. 2009 | academic association | Publication of an observational study[36]<br>The follow-up survey showed that surgical treatment might be useful for BRONJ when performed at the appropriate time, and BRONJ was shown to be refractory because only nine of 17 cases were cured in these 2 years. |
| May 2010 | academic association, pharmaceutical manufacturers | Publication of a position paper[37] |
| June 2010 | PMDA | Measure: revised package inserts for alendronate, risedronate and etidronate<br>"ONJ has been reported in patients receiving bisphosphonates, regardless of the route of administration. Treating physicians should advise their patients to undergo dental examinations and to finish any invasive dental procedures, such as tooth extraction, if necessary, prior to treatment with BPs. While on treatment with BPs, these patients should have regular dental consultations and avoid invasive dental procedures." |
| Sep. 2010 | academic association | Publication of a book, entitled "The utility and osteonecrosis of the jaw of BPs" |
| Sep. 2010 | PMDA | Release of safety measures ("The progress of assessments and measures regarding BP-related osteonecrosis of the jaw"), including a survey of the number of cases of BP-related osteonecrosis of the jaw and an outline of the individual case reports reported to PMDA |

*The date indicates the first dissemination of safety information.
†PMDA: Pharmaceuticals and Medical Devices Agency.

65.0), and 2794 patients received other osteoporosis drugs (40.3%; mean age, 65.5). The median durations of administration were 364.0 days for BPs and 439.5 days for other osteoporosis drugs. For the BP group and the other osteoporosis drugs group, the numbers of patients using concomitant steroids were 2934 (71.0%) and 1508 (53.9%), respectively; the numbers of patients treated with anti-cancer drugs were 551 (13.3%) and 256 (9.1%), respectively; and the numbers of patients with diabetes were 707 (17.1%) and 442 (15.8%), respectively.[18]

The number of BP users has been increasing steadily since 2000 (Figure 2). The number of estrogen users, including users of selective estrogen receptor modulators, has been low. The number of users of other osteoporosis medications, including active vitamin D3 or calcium,

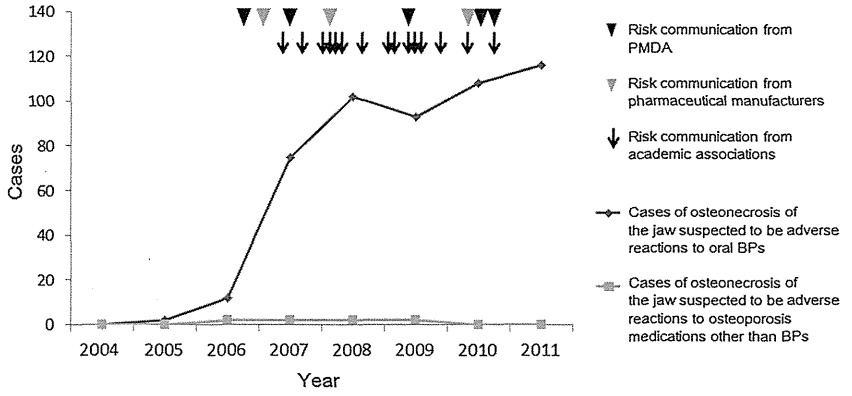



Figure 1. Trends in the number of ONJ cases per year reported to the Drug Adverse Reactions Reporting System of the PMDA and risk communication activities. Legend: The cases of ONJ that were suspected adverse reactions to oral bisphosphonates and those that were suspected adverse reactions to other agents for osteoporosis, reported to the Drug Adverse Reactions Reporting System of the PMDA, are shown as a dark gray line and a light gray line, respectively. Black arrowhead: risk communication from the PMDA; gray arrowhead: risk communication from pharmaceutical manufacturers; arrow: risk communication from academic associations

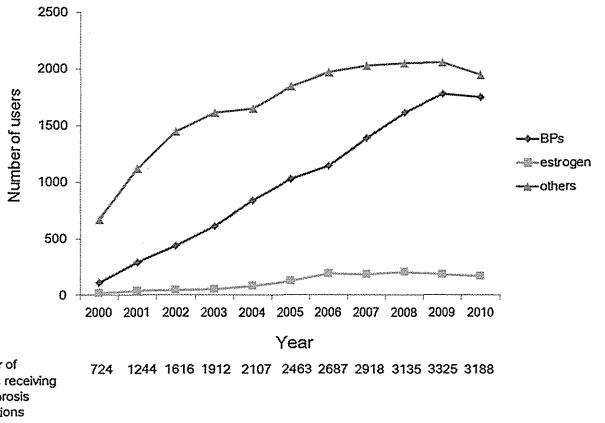



Figure 2. The number of patients prescribed each agent for osteoporosis in the cohort. Legend: The numbers of patients prescribed bisphosphonates, estrogen and a selective estrogen receptor modulator, as well as other agents for osteoporosis, each year in a cohort of 6293 osteoporosis patients are illustrated with a dark gray line of diamonds, a gray line of triangles and a light gray line of squares, respectively. The year 2000 contains 2 months, and the year 2010 contains 10 months. The numbers of patients receiving osteoporosis medications in each year are shown below the graph

increased before 2006 and since then has remained approximately constant.

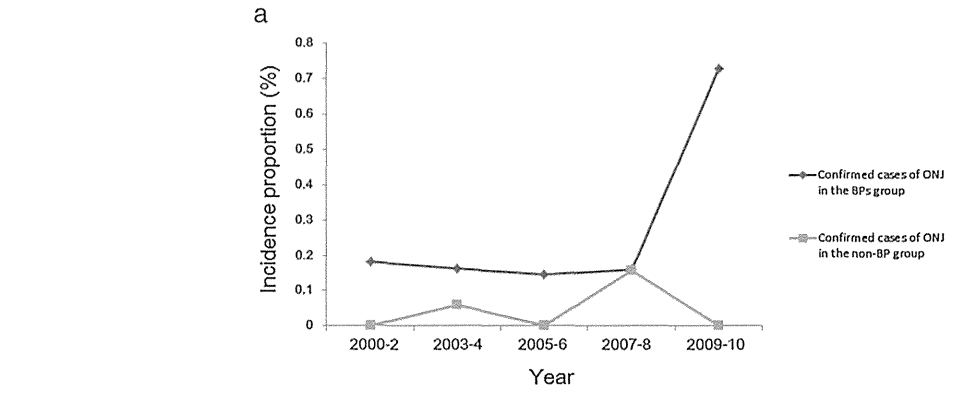
The EMRs of a total of 1987 patients with records of ONJ or inflammatory conditions of the jaw that were possibly related to ONJ were manually reviewed, and 46 patients were confirmed to have ONJ.[18]

The incidence proportion of confirmed ONJ in the BP group increased approximately four-fold in 2009 and 2010, compared with the pre-2009 level. The incidence proportion of confirmed ONJ in the non-BP group remained low (Figure 3a). Both of the incidence proportion of confirmed ONJ cases and that of inflammatory conditions of the jaw increased after 2009; however, the increase in inflammatory conditions of the jaw was not as high as that of confirmed cases (Figure 3b). This measure was therefore not a good surrogate for confirmed ONJ in this study.

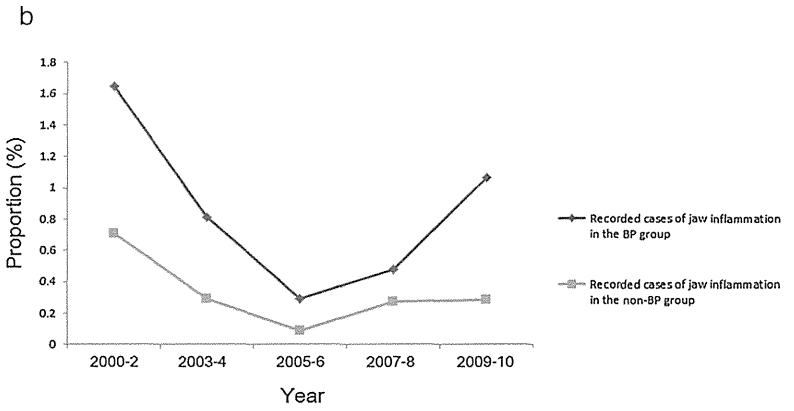
## DISCUSSION

Risk communication efforts by pharmaceutical manufacturers and academic associations began within 1 year after the package insert was revised in October 2006, and ONJ was increasingly reported to the PMDA within 1 year. In our cohort, the incidence proportion of ONJ, diagnosed according to standardized criteria, increased in 2009 and in later years. During this period, BPs were frequently prescribed, and there were no increases in the use of alternative agents, such as selective estrogen receptor modulators.

Physicians' case reports regarding ONJ in 2003[4,5] in the USA led to revisions of package inserts in 2004 to 2005.[7,25,26] In Japan, the pharmaceutical manufacturers revised the package inserts for intravenous BPs in 2005 and for oral BPs in 2006 and 2007, but the revision was delayed for 2 years after the revision in the USA. The physicians' case reports regarding ONJ were first published in 2007, 4 years after their publication in the USA; thus, the physicians' reports in Japan did not contribute to the increased suspicion of ONJ related to BPs or to the revision of the package insert. Academic associations were rather active in risk communication in the later dissemination phase. Physicians and academic associations have been able to detect new safety concerns for marketed drugs and to conduct epidemiological studies effectively, and we should reconsider academic associations, as well as the regulatory authority




| | | | | | |
|---|---|---|---|---|---|
| BP group | 546 | 1234 | 2054 | 3143 | 4129 |
| Confirmed cases of ONJ in the BP group | 1 | 2 | 3 | 5 | 30 |
| Non-BP group | 1272 | 1702 | 2236 | 2564 | 2794 |
| Confirmed cases of ONJ in the non-BP group | 0 | 1 | 0 | 4 | 0 |




| | | | | | |
|---|---|---|---|---|---|
| BP group | 546 | 1234 | 2054 | 3143 | 4129 |
| Recorded cases in the BP group | 9 | 10 | 6 | 15 | 44 |
| Non-BP group | 1272 | 1702 | 2236 | 2564 | 2794 |
| Recorded cases in the non-BP group | 9 | 5 | 2 | 7 | 8 |

Figure 3. (a). The incidence proportion of confirmed cases of ONJ in the cohort. Legend: The incidence proportions of the confirmed ONJ cases in 100 BP-group patients in 2000–2002, 2003–2004, 2005–2006, 2007–2008 and 2009–2010 are indicated by a dark gray line of diamonds. The incidence proportions of confirmed ONJ cases per 100 non-BP-group patients in each 2- to 3-year period are indicated by a light gray line of squares. The number of patients in the BP group, the number of confirmed ONJ cases in the BP group, the number of patients in the non-BP group and the number of confirmed ONJ cases in the non-BP group are shown below the graph. (b). The proportions of recorded ONJ cases in the cohort. Legend: The proportions of recorded cases of inflammatory conditions of the jaw in 100 BP-group patients in 2000–2002, 2003–2004, 2005–2006, 2007–2008 and 2009–2010 are indicated by a dark gray line of diamonds. The proportions of recorded cases of inflammatory conditions of the jaw in 100 non-BP-group patients in each 2- to 3-year period are indicated by a light gray line of squares. The number of patients in the BP group, the number of recorded cases of inflammatory conditions of the jaw in the BP group, the number of patients in the non-BP group and the number of recorded cases of inflammatory conditions of the jaw in the non-BP group are shown below the graph

and pharmaceutical manufacturers, as resources for monitoring and minimization of the risks of medicines and for ensuring the accuracy of information.

We evaluated the impact of risk communications by analyzing the prescriptions of medications for osteoporosis and the incidence proportion of ONJ. The use of BPs increased steadily, but the prescriptions for BPs were not influenced by the risk communications in this study. BPs are among the most established drug types for the treatment of osteoporosis in postmenopausal women,[27] and the gradual increase in the use of BPs over the periods, before and after the dissemination of the safety information, was reasonable considering the risk–benefit balance. We could not determine whether the physicians prescribed BPs after considering the risk–benefit balance or simply did not receive the safety information. Many confounding factors can influence the prescription of BPs, such as the active participation of academic associations or the perceptions of physicians and patients toward adverse events. Physicians might hesitate to change prescribing habits because of known obstacles, such as the lack of time during outpatient care and the desire to maintain trust in the physician–patient relationship.[28]

The rapid increase in the cases of ONJ that were suspected adverse reactions to oral BPs reported to the regulatory authority after the risk communications efforts might indicate that the primary cause of the increase was awareness of the disease because the increase was quite sharp. The incidence proportion of ONJ in the BP group increased in our cohort, although the increase occurred 3 years after the risk communications began. There would have been few missed or misdiagnosed cases of ONJ in our cohort because the cases were diagnosed based on an extensive manual review of the EMRs, using well-established criteria. There might have been other causes for the increase in the incidence proportion of ONJ in our cohort in addition to risk communication; one possibility is the longer exposure to BPs[8,29] in the cohort. Longer exposure and risk communication occurred simultaneously; therefore, we could not distinguish the impact of risk communication from that of longer exposure. There was a time difference between the increase in the number of cases of ONJ reported in the Drug Adverse Reactions Reporting System and the increase in the incidence proportion of ONJ in the cohort. The cases of ONJ reported to the Drug Adverse Reactions Reporting System include past cases of ONJ: cases that occurred before 2006 might be reported as cases of ONJ after 2006. Moreover, the diagnosis of ONJ is not standardized and might include other inflammatory conditions of the jaw. However, the number of ONJ patients in the cohort reflects the number of active ONJ patients diagnosed in the hospital. The difference between the recording and the diagnosis of ONJ most likely resulted in the time difference.

Previous reviews have found it difficult to estimate the average effect of risk communication on clinical practice[16,17,30] because of heterogeneity in the study designs, analyses, outcome measurements, therapeutic areas and types of communication. ONJ can be reduced with preventive measures, including clinical oral examinations and good oral hygiene.[31,32] Unfortunately, we did not observe a decrease in the incidence proportion of ONJ in our cohort during this study period, which would have been the clinical outcome. Additional appropriately designed research is warranted to understand the effects of past communications strategies and to estimate the impact of future communication.

The limitations of our study are described below. First, factors other than safety information collected in our study, such as pharmaceutical use, could have simultaneously influenced the incidence proportion of ONJ. Second, we did not consider the scale, the duration or the content of the risk communication; it is therefore not possible to evaluate the impact of each risk communication material quantitatively. Third, the data on drug use and on the incidence proportion of ONJ in Kyoto University Hospital were limited to a single institution in Japan; thus, the generalizability of the results cannot be assured. The much higher incidence of ONJ in our study compared to the published literature might be explained by the inclusion of numerous steroid users, older patients and inpatients. Moreover, the cohort study was subject to a referral bias toward the selection of more severe cases, given that our department is the lead institution for oral and maxillofacial surgery in Kyoto City, as discussed in our previous report.[18] We could not account for BP exposure that occurred before consultation at Kyoto University Hospital, which might have affected the incidence proportion of ONJ. Finally, this study was retrospective, using a database derived from the EMRs, and the data were not as accurate and consistent as they would have been in a prospective study.

## CONCLUSION

The use of oral BPs increased in osteoporosis patients, regardless of the safety notifications concerning ONJ related to BPs. ONJ was increasingly diagnosed after the dissemination of safety information about BP-related ONJ using repetitive and mixed communication methods; the impact of these communications materials was not clear. Our evaluation of the risk communication materials suggests that appropriate cooperation models involving the parties concerned with pharmacovigilance should be planned for the dissemination of safety information and for the delivery and evaluation of new safety concerns with marketed drugs.

## CONFLICT OF INTEREST

Eriko Sumi collected information on when, how and what type of risk communications regarding osteonecrosis of the jaw were released from pharmaceutical companies.

KEY POINT

- The use of oral bisphosphonates (BPs) in osteoporosis patients has increased regardless of safety concerns about osteonecrosis related to BPs. Osteonecrosis of the jaw was increasingly diagnosed after risk communication; however, the impact of the risk communication was not clear. Safety notifications were disseminated diligently after the package insert was revised. However, there was no surveillance for osteonecrosis of the jaw before the revision.

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web-site:

Appendix 1. List of drugs studied in cases of OMJ reported to the regulatory authority

Appendix 2. List of International Classification of Diseases (ICD-10) code for osteoporosis studied in the cohort study

Appendix 3. List of drugs studied in the cohort study

Appendix 4. List of International Classification of Diseases (ICD-10) code for inflammatory conditions of the jaw studied in the cohort study