重症多形滲出性紅斑の眼後遺症に対する
輪部支持型ハードコンタクトレンズCS-100の
臨床試験

自ら治験を実施する者

京都府立医科大学
視覚機能再生外科学
外 園 千 恵

重症多形滲出性紅斑
（SJS: Stevens-Johnson症候群およびTEN:中毒性表皮壊死症）
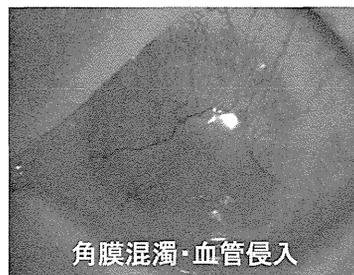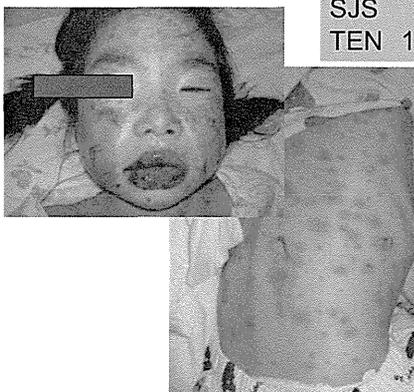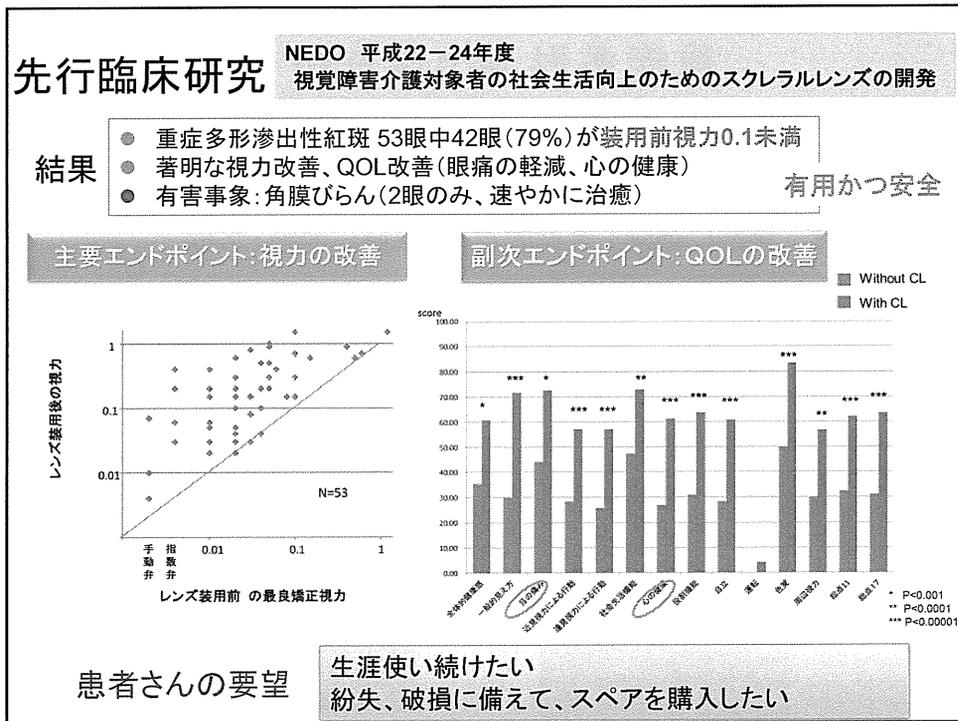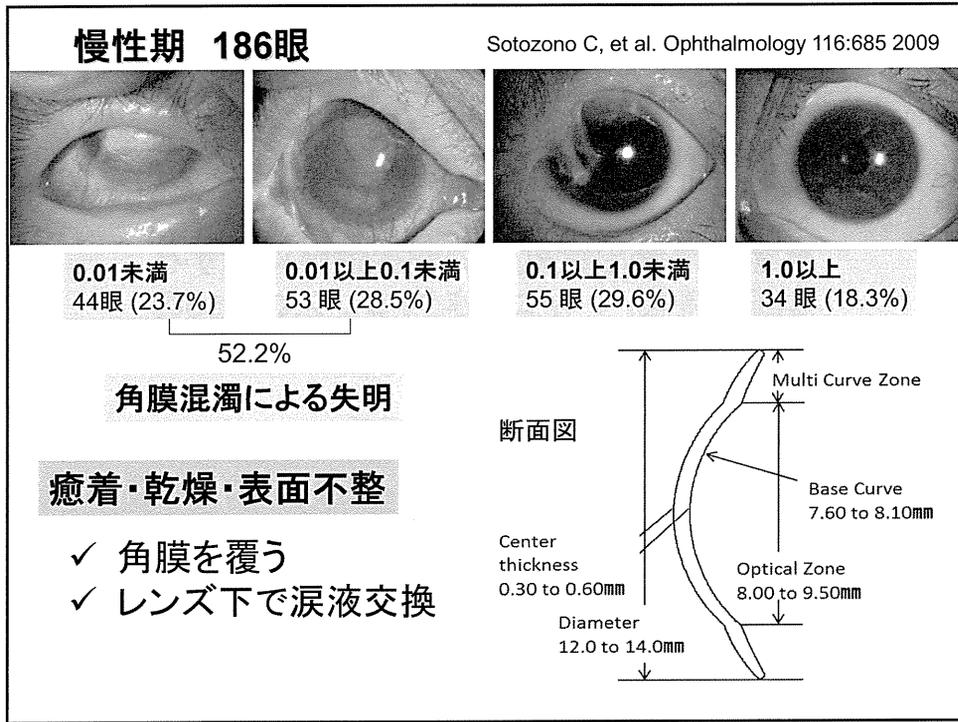
● 人口100万人あたり、1年に2-6名程度の発症
● 突然に高熱、全身の皮膚・粘膜に発疹・水疱

急性期

致死率
SJS　8%
TEN　19%

慢性期

✓ 視覚障害・高度ドライアイ
✓ 若年者が多い

角膜混濁・血管侵入

1

慢性期　186眼

Sotozono C, et al. Ophthalmology 116:685 2009

| 0.01未満 44眼 (23.7%) | 0.01以上0.1未満 53眼 (28.5%) | 0.1以上1.0未満 55眼 (29.6%) | 1.0以上 34眼 (18.3%) |

52.2%

角膜混濁による失明

癒着・乾燥・表面不整

✓ 角膜を覆う
✓ レンズ下で涙液交換

断面図

Multi Curve Zone

Base Curve
7.60 to 8.10mm

Center thickness
0.30 to 0.60mm

Optical Zone
8.00 to 9.50mm

Diameter
12.0 to 14.0mm

先行臨床研究

NEDO　平成22－24年度
視覚障害介護対象者の社会生活向上のためのスクレラルレンズの開発

結果
● 重症多形滲出性紅斑　53眼中42眼（79%）が装用前視力0.1未満
● 著明な視力改善、QOL改善（眼痛の軽減、心の健康）
● 有害事象：角膜びらん（2眼のみ、速やかに治癒）

有用かつ安全

主要エンドポイント：視力の改善

副次エンドポイント：QOLの改善

Without CL
With CL

* P<0.001
** P<0.0001
*** P<0.00001

N=53

患者さんの要望

生涯使い続けたい
紛失、破損に備えて、スペアを購入したい

開発スケジュール

	H22-24年度	H25.4	H25.9		H26.4	H26.9	H27.4

試験物製造　試作品製作　済　試験物QMS製造、供給

臨床・治験　先行臨床研究　済　解析・結果まとめ　済　医師主導治験　解析・総括報告書

科研費採択　治験体制整備　オーファン申請　承認申請

薬事　規制当局との面談、折衝

海外連携先への国際展開

Now!

本研究の特徴

- 希少かつ難治性疾患
- 他に有効な治療法がない

5

実施体制

研究代表者・治験責任医師：外園（府立医大）
研究分担者： 今井（府立医大）
　　　　　　　角（京大）、上田（同志社・府立医大）
医師主導治験事務局：2名（CRC実務担当＋事務局業務担当）

サンコンタクト
治験機器提供

府立医大
治験の実施・体制整備

TRI
調整業務・コンサル

京都大学
SOP・体制整備支援・PM業務
治験の実施

CRO
業務委託先

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3

連携機関

サンコンタクトレンズ

> 治験機器提供者
> （承認後、製造販売引受業者）

神戸TRI

> CE取得資料とハーモナイズした
> 国内治験準備
> グローバル臨床試験に関する
> プロジェクトマネジメント

京都大学

> 共同開発協定（京都府立-京大）
> に基づく業務連携
> 橋渡しNWシーズC（連携シーズ）
> とすることを準備中（H26度より）

CRO業務委託

> 株式会社　Bell Medical Solutions
>
> ✓ モニタリング
> ✓ データマネージメント
> ✓ 統計解析
> ✓ 総括報告書

> 株式会社　シミックホールディングス
> ✓ 監査

目標　医師主導治験を実施、医療機器として承認

対象疾患

重症多形滲出性紅斑
（SJS）

試験物の名称

輪部支持CL（コンタクトレンズ）

プロトコール骨子

研究機関	京都府立医科大学
対象	重症多形滲出性紅斑
目標症例数	（相談）
エンドポイント	1）視力改善
	2）QOL改善
患者リクルート	

SJS患者会（約130名）
京府医大データベース（約220名）
（日本眼科学会　患者レジストリー）

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概要

治験課題名	重症多形滲出性紅斑の眼後遺症に対する輪部支持型 ハードコンタクトレンズCS-100の臨床試験
治験の目的	重症多形滲出性紅斑の眼後症を対象として輪部支持型 ハードコンタクトレンズCS-100の有効性及び安全性を確認する。
治験デザイン	非対照、オープンラベル試験
対象	重症多形滲出性紅斑の眼後遺症を有する患者
目標被験者数	12　例
治験期間	同意取得から装用開始後13週間

選択基準

1. 重症多形滲出性紅斑による眼後遺症を有する。
2. 最良矯正視力が0.01以上0.7未満である。
3. シルマーテストI法にて5ミリ以下である。
4. 登録時の年齢が20歳以上75歳未満である。
5. 外来に通院可能である。
6. 試験参加について、患者本人から文書による同意が得られている

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観察・検査項目

検査項目	装用開始前*1	装用期 1日目	2週目*2 (±1週間)	4週目 (±1週間)	8週目 (±1週間)	13週目 (±2週間)	中止時
被験者背景	○						
自覚症状	○	○	○	○	○	○	○
VFQ-25調査	○					○	○
VAS調査	○			○		○	○
眼後遺症のグレーディング	○						
涙液分泌量検査(シルマーテスト法)	○						
前眼部検査 (細隙灯顕微鏡検査)	○	○*3	○*3	○*3	○*3	○*3	○*3
視力検査*4 (5m視力表法)	○	○	○	○	○	○	○
眼圧検査	○					○	○
レンズフィッティング検査		○	○	○	○	○	
不具合情報(レンズ検査、問診)		←――――――――――――――→					
有害事象情報		←――――――――――――――→					
装用情報		←――――――――――――――→					
中止情報							○

*1：装用開始前4週間以内に評価を行う。
*2：2週目とは、装用開始日を1日目とした場合の15日目をいう。
*3：前眼部検査は、毎回、CL装用及びCLを外した状態の両方を観察する。

有効性 主要評価項目	治験レンズ補正による最良矯正視力の変化
有効性 副次評価項目	(1) 自覚症状の変化（NEI VFQ-25調査） (2) 目の痛みの程度及び目の乾燥の程度の変化（VASによる調査） (3) 視力改善率（logMAR換算値として0.2以上の改善を得た割合）
安全性 評価項目	(1) 有害事象の発現 (2) 不具合の発現
統計手法	有効性評価項目に関する変化の有意性の検定には、Wilcoxon符号付順位検定を用いる。検定の有意水準は、10%とする。 変化の有意性を経時的に検討する場合には、同様の解析を行う。 検定を行わないデータについては、計量尺度については要約統計量として例数、平均値、標準偏差、最小値、最大値及び中央値を求める。分類尺度及び順序分類尺度については、各分類に含まれる例数及び割合を算出する。
治験実施予定 期間	2014年4月1日〜2015年3月31日

予測される主な有害事象　　　角膜びらん、角膜感染症、眼痛
予測される主な不具合　　　　コンタクトレンズの破損、紛失

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相談内容

相談内容1
* 　本治験における主要エンドポイントを視力補正とすることが適切であることを確認したい。

相談内容2
* 　本治験におけるコンタクトレンズ装用後の観察期間を13週間と設定することが適切であることを確認したい。

相談内容3
* 　目標症例数を実施可能な例数（10例程度）と設定することが、受け入れ可能であることを確認したい。

相談内容4
* 　薬事申請のデータパッケージについて確認したい。

照会・回答での主な議論

* 選択基準
  * 視力　0.01以上0.6以下

* 主要評価項目
  * 視力の変化
  * 視力改善率は副次評価項目に

7

TRIALS

RESEARCH   Open Access

The correlation between the number of eligible patients in routine clinical practice and the low recruitment level in clinical trials: a retrospective study using electronic medical records

Eriko Sumi[1*], Satoshi Teramukai[2], Keiichi Yamamoto[3], Motohiko Satoh[4], Kenya Yamanaka[4] and Masayuki Yokode[1]

Abstract

Background: A number of clinical trials have encountered difficulties enrolling a sufficient number of patients upon initiating the trial. Recently, many screening systems that search clinical data warehouses for patients who are eligible for clinical trials have been developed. We aimed to estimate the number of eligible patients using routine electronic medical records (EMRs) and to predict the difficulty of enrolling sufficient patients prior to beginning a trial.

Methods: Investigator-initiated clinical trials that were conducted at Kyoto University Hospital between July 2004 and January 2011 were included in this study. We searched the EMRs for eligible patients and calculated the eligible EMR patient index by dividing the number of eligible patients in the EMRs by the target sample size. Additionally, we divided the trial eligibility criteria into corresponding data elements in the EMRs to evaluate the completeness of mapping clinical manifestation in trial eligibility criteria into structured data elements in the EMRs. We evaluated the correlation between the index and the accrual achievement with Spearman's rank correlation coefficient.

Results: Thirteen of 19 trials did not achieve their original target sample size. Overall, 55% of the trial eligibility criteria were mapped into data elements in EMRs. The accrual achievement demonstrated a significant positive correlation with the eligible EMR patient index ($r = 0.67$, 95% confidence interval (CI), 0.42 to 0.92). The receiver operating characteristic analysis revealed an eligible EMR patient index cut-off value of 1.7, with a sensitivity of 69.2% and a specificity of 100.0%.

Conclusions: Our study suggests that the eligible EMR patient index remains exploratory but could be a useful component of the feasibility study when planning a clinical trial. Establishing a step to check whether there are likely to be a sufficient number of eligible patients enables sponsors and investigators to concentrate their resources and efforts on more achievable trials.

Keywords: Clinical trials, Research patient recruitment, Eligibility determination, Clinical informatics, Accrual

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Background

Clinical trials are essential for gaining and extending knowledge about new therapies, and sufficient patient enrollment in clinical trials is critical to fulfill their scientific objectives. Nevertheless, a number of trials have failed to achieve their target sample size within the original accrual period [1-3]. For such trials, extending the accrual period, modifying the eligibility criteria or, in the worst case scenario, prematurely closing the trial may be necessary. Moreover, many investigators continue to make the same mistakes despite the great advances made in handling clinical trials data using information technology [4].

Many reasons for the low levels of recruitment have been cited, including fewer eligible patients than expected, a smaller percentage of patients agreeing to participate [1,5], time constraints, resource issues, consent interviews and difficulties in identifying the patients [6].

Recently, many screening systems that search electronic medical records (EMRs) or clinical data warehouses derived from EMRs for patients eligible for clinical trials have been developed, and their efficiencies have been evaluated [7-9]. The number of patients who meet the eligibility criteria when medical records are manually reviewed is less (13 to 74%) than the number of potential trial patients identified by an electronic screening system [7,10-15]. Nevertheless, screening systems are promising in that they can provide information on the total eligible patient population at the planning stage of a clinical trial. Estimates of the number of eligible patients enable both the sponsors and the investigators to concentrate their resources and efforts on more achievable and conclusive trials. Moreover, investigators should not put their patients at risk by enrolling them in an inconclusive trial. For more reasonable research programs, we hypothesized that researchers can predict the difficulty of trial patient enrollment by estimating the number of eligible patients using EMR data. We explored how to estimate the number of eligible patients using the EMRs, and using a retrospective design, we tested our hypothesis that the number of eligible patients identified from EMRs correlates with the number of patients actually enrolling in clinical trials.

Methods

Trial data collection

The trials were identified using a departmental database from the Institute for Advancement of Clinical and Translational Science and the University Hospital Medical Information Network Clinical Trial Registry (UMIN-CTR) [16]. The investigator-initiated therapeutic trials that started between July 2004 and January 2011 were included if the following data were available: the trial eligibility criteria, target sample size, number of enrolled patients and accrual period at the Kyoto University Hospital (KUH). The trial eligibility criteria, number of scheduled and enrolled patients and the duration of enrollment were extracted from published papers or from registered information in the UMIN-CTR. For unpublished data, trial protocols and management lists in the departmental database were used after obtaining consent from the relevant principal investigators. The study protocol was approved by the Ethical Committee of the Graduate School of Medicine, Kyoto University (E1175).

Electronic medical records retrieval system

We used an EMR retrieval system that was developed at the Institute for Advancement of Clinical and Translational Science to screen EMRs for patients in KUH [17]. In this system, EMR data, including diagnoses, medications and injections, laboratory tests, radiological or pathological studies, and operative notes, were extracted from the data warehouse to enable the comprehensive and efficient retrieval of patient data.

The replacement of trial eligibility criteria with patient characteristics for a comparison to electronic medical records

We replaced the trial eligibility criteria of the trial protocol with patient characteristics that could be easily compared with EMR data and matched the translated criteria with the data elements in EMRs, referencing the methods of previous studies [10,11,17-21].

After the trial eligibility criteria were collected, three physicians discussed and replaced concepts in the eligibility criteria of each trial with patient characteristics, which were represented by codes, fixed terms or numeric data. Some medical concepts, such as 'severe heart disease', may be interpreted differently depending on the trial and the clinician caring for the patients. The three physicians discussed these concepts and made a general list of how to interpret these concepts as patient characteristics, such as considering a particular concept to be part of a group of diagnoses. The list also included instructions on how to replace the specific medical conditions that do not directly indicate one or more data elements in the EMRs by the data elements in the EMRs related to the conditions. For instance, we replaced the criterion 'patients who do not need intravenous hyperalimentation' with 'no order for high-calorie infusion'. Namely, we aimed to estimate the number of patients who were already receiving care from the trial treatment or from alternative treatments in routine clinical practice rather than estimating the potential number of eligible patients still at the diagnostic stage. Concurrently, we re-categorized the eligibility criteria of the trial protocol into three categories: 'Select', 'Omit' and 'Not applicable'. The 'Select' category indicates that the patient was

included if he or she fulfilled the condition. The 'Omit' category indicates that the patient was excluded if he or she fulfilled the condition but was not excluded if the data were not available or were missing. The 'Not applicable' category indicates that the criterion cannot be searched in the EMRs because of missing or incomplete EMR data; for instance, the data were entered in plaintext freely, were captured as an image or were not entered. Thus, the items in the 'Not applicable' category were neither translated into computable eligibility criteria nor searched for in the EMRs.

Laboratory test requirements were indicated in either the inclusion or exclusion items of the trial eligibility criteria. If the laboratory tests were routinely performed, the requirements of the laboratory tests were categorized as 'Select', and if the test result fulfilled the requirement at least once, the patients were deemed eligible. If the tests were not performed routinely, the requirements of the laboratory tests were categorized as 'Omit'.

The periods of the order or the records to search were critical for estimating the number of patients. We searched for eligible patients using a primary criterion that was recorded during the year for which we wanted to know the number of eligible patients. For the other criteria, such as acute illness or diseases with no prior therapy, we searched eligible patients with other criteria in addition to the primary criterion recorded during the preceding two years for acute illness or diseases with no prior therapy and the previous five years for chronic or recurrent disease.

The degree of concordance with the electronic medical record data

We examined how many and what type of trial eligibility criteria were mapped into the patient characteristics and corresponding data elements of the EMRs to evaluate the completeness of our mapping. We assigned patient characteristics, as mentioned above, to one of the 27 semantic categories defined by Luo et al. [22]. One author, a medical doctor, broke up and assigned the eligibility criteria to one of the semantic categories, and another medical doctor validated the results. Then, we counted the number of patient characteristics in the 'Select' or 'Omit' and 'Not applicable' categories.

The number of eligible patients in the electronic medical records

We searched for potentially eligible patients using the EMR retrieval system. Each query in the EMR retrieval system was tested to find errors both in the program and in the search results. A system engineer then examined the number of patients in the 'Select' category, the 'Select' but not the 'Omit' category and the 'Select' and 'Omit' categories to confirm that the first number was equal to the sum of the second and third numbers. After

this test, he obtained the estimated number of potentially eligible patients both in the year preceding the start of a trial and in the year in which a trial started using the EMR retrieval system. We did not perform an additional manual review of the medical records after the data extraction.

Statistical analysis

The target sample size, number of patients actually enrolled, scheduled accrual period and actual accrual period were obtained.

The following formula was used to determine the eligible EMR patient index and the accrual achievement:

The eligible EMR patient index = the number of eligible patients identified by the EMRs per year/the target sample size per year.
The accrual achievement = the number of enrolled patients per year/the target sample size per year.
Where, the target sample size per year = the target sample size at KUH/the scheduled accrual period (year).
The number of enrolled patients per year = the number of patients actually enrolled at KUH/the actual accrual period (year).

We examined the relationship between the eligible EMR patient index and the accrual achievement using Spearman's rank correlation coefficient. The receiver operating characteristic (ROC) curves were used to determine the cut-off value for the eligible EMR patient index that identified the low enrollment trials with accrual achievements <1.0. Furthermore, we examined the consistency between the numbers of searched eligible patients in the year preceding the start of a trial and in the year in which a trial began to evaluate the reliability of the eligible EMR patient index. All statistical analyses were performed using R-2.14.1 and SAS software for Windows.

Results
Trial information

Of the 24 trials screened, 15 trials in the Institute for Advancement of Clinical and Translational Science database met the inclusion criteria, in addition to four trials in the UMIN-CTR (accessed on May 2, 2011). Table 1 indicates the characteristics of the 19 trials. The patient accrual period was extended in seven trials, and six trials recruited 100% or more of their target sample size within the scheduled accrual period.

The replacement of trial eligibility criteria with patient characteristics for comparisons with the electronic medical records

We replaced and matched the trial eligibility criteria for the 19 trials with the data elements in the EMRs. We

Table 1 Characteristics of the trials

Characteristic	Number of trials
Phase	
I/II	7
II	6
IV	1
Not specified	5
Clinical areas	
Cancer	6
Internal medicine	6
Orthopedics	5
Others	2
Participating centers	
KUH only	17
Multicenter study	2
Study start date	
2004 to 2005	3
2006 to 2007	10
2008 to 2009	3
2010	3
Target sample size per year per center[a]	
0 to 9	6
10 to 19	6
20 to 29	2
30 to 39	1
≥40	4
Enrolled patients per year per center ·	
0 to 9	10
10 to 19	3
20 to 29	1
30 to 39	4
≥40	1

[a]The target sample size was calculated as the total sample size divided by the number of centers in a single trial for which an assigned sample size was not determined. KUH, Kyoto University Hospital.

present an example of this process in a trial titled 'A randomized controlled study of the effectiveness of transcatheter arterial chemoembolization with cisplatin and transcatheter arterial chemoembolization with epirubicin for multiple hepatocellular carcinomas' (Figure 1). The trial candidates were patients who were to receive transcatheter arterial chemoembolization for multiple HCCs at stage 2 to 4a without thrombosis in the portal vein, hepatic vein and the bile duct, although the trial eligibility criteria were only presented as the disease conditions. Therefore, we replaced the disease condition with the related standard treatment for the patients and assessed

the radiologic study order in EMRs to narrow down the trial candidates.

The degree of matching with the electronic medical record data

The 318 eligibility criteria from the 19 trials were transformed into 425 patient characteristics. Of the 425 patient characteristics, 408 were related to 18 semantic categories, and 17 were related to a ' no fitting category'. We found that 55% (235 of 425) of the characteristics in the eligibility criteria were matched with data elements in the EMRs. Compared with a previous study by Kopcke *et al.* [21], the degree of matching was similar with respect to both the total and the category (Table 2). The degree of match for each trial ranged from 38% to 75% (median 54%), and the degree was 50% in three trials.
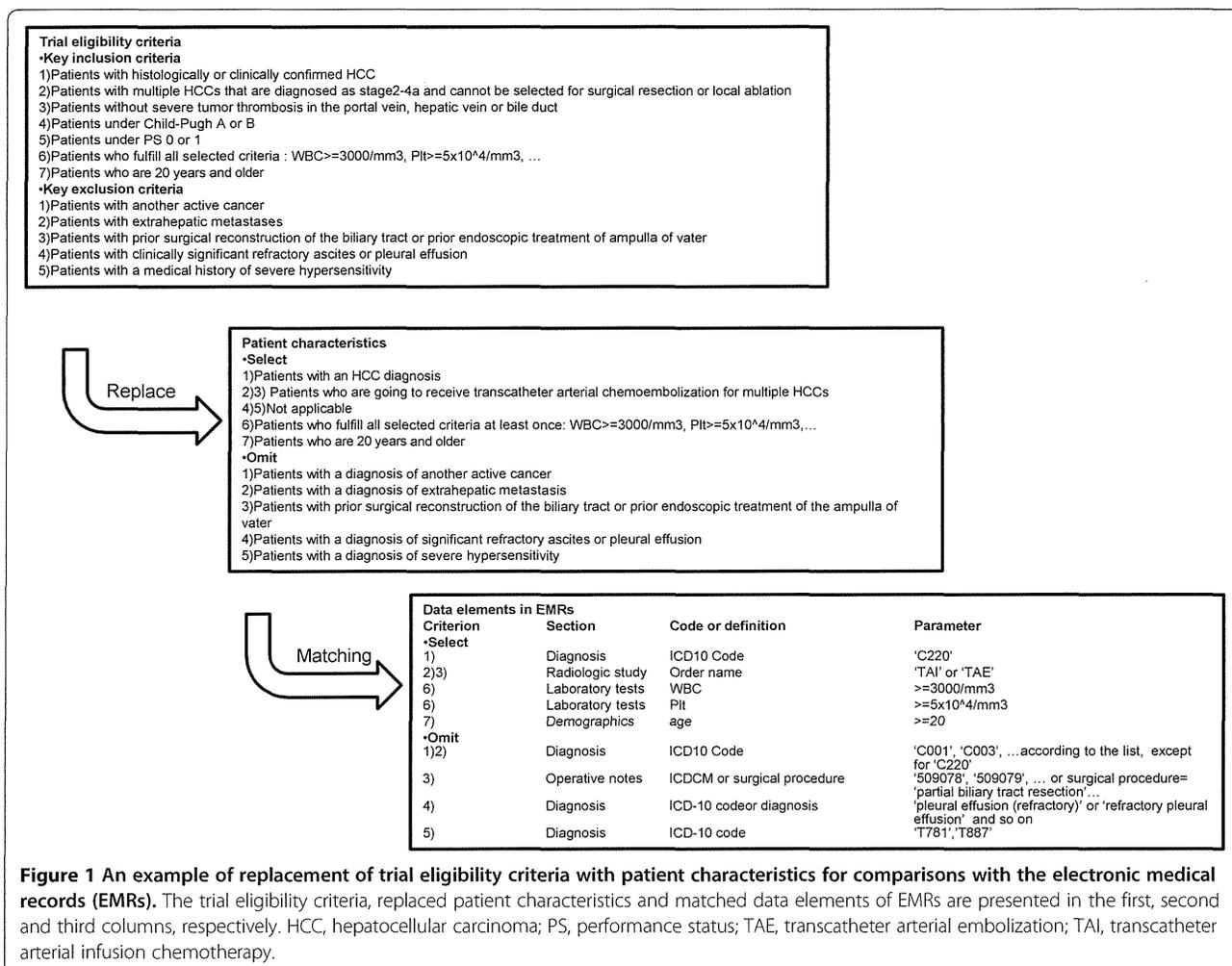
Data retrieval, correlation and receiver operating characteristic analysis

We searched the EMRs for patients who fit the computable criteria characteristics in the 19 trials, counted the number of patients in each trial and calculated the eligible EMR patient index. The accrual achievement demonstrated a significant positive correlation with the eligible EMR patient index (r = 0.67, 95% confidence interval (CI), 0.42 to 0.92; Figure 2). The ROC analysis revealed an estimated 1.7 cut-off value for the eligible EMR patient index, with an area under the curve (AUC) of 0.846, a sensitivity of 69.2% and a specificity of 100.0% (Figure 3). None of the nine trials for which the eligible EMR patient index was less than 1.7 achieved their original target sample size within the scheduled accrual period. There were 16 trials in which 50% or more of trial criteria were matched with the data elements in the EMRs. The relationship of the eligible EMR patient index and the accrual achievement in these 16 trials also exhibited a positive correlation (r = 0.67, 95% CI, 0.38 to 0.96). The ROC analysis revealed an estimated 1.7 cut-off value for the eligible EMR patient index, with an AUC of 0.867, a sensitivity of 70.0% and a specificity of 100.0%.

The number of identified eligible patients in the year preceding the start of the trial was almost consistent with the number of identified eligible patients in the year in which a trial began (Figure 4). The median ratio of the number of eligible patients in the preceding year to the number in the year a trial began was 1.00 (range, 0.36 to 1.67).

Discussion

We developed a formula to estimate the number of eligible patients using routine EMR data. In half of the tested trials, using the eligible EMR patient index, we

Trial eligibility criteria
·Key inclusion criteria
1)Patients with histologically or clinically confirmed HCC
2)Patients with multiple HCCs that are diagnosed as stage2-4a and cannot be selected for surgical resection or local ablation
3)Patients without severe tumor thrombosis in the portal vein, hepatic vein or bile duct
4)Patients under Child-Pugh A or B
5)Patients under PS 0 or 1
6)Patients who fulfill all selected criteria : WBC>=3000/mm3, Plt>=5x10^4/mm3, ...
7)Patients who are 20 years and older
·Key exclusion criteria
1)Patients with another active cancer
2)Patients with extrahepatic metastases
3)Patients with prior surgical reconstruction of the biliary tract or prior endoscopic treatment of ampulla of vater
4)Patients with clinically significant refractory ascites or pleural effusion
5)Patients with a medical history of severe hypersensitivity

Replace

Patient characteristics
·Select
1)Patients with an HCC diagnosis
2)3) Patients who are going to receive transcatheter arterial chemoembolization for multiple HCCs
4)5)Not applicable
6)Patients who fulfill all selected criteria at least once: WBC>=3000/mm3, Plt>=5x10^4/mm3,...
7)Patients who are 20 years and older
·Omit
1)Patients with a diagnosis of another active cancer
2)Patients with a diagnosis of extrahepatic metastasis
3)Patients with prior surgical reconstruction of the biliary tract or prior endoscopic treatment of the ampulla of vater
4)Patients with a diagnosis of significant refractory ascites or pleural effusion
5)Patients with a diagnosis of severe hypersensitivity

Matching

Data elements in EMRs

Criterion	Section	Code or definition	Parameter
·Select			
1)	Diagnosis	ICD10 Code	'C220'
2)3)	Radiologic study	Order name	'TAI' or 'TAE'
6)	Laboratory tests	WBC	>=3000/mm3
6)	Laboratory tests	Plt	>=5x10^4/mm3
7)	Demographics	age	>=20
·Omit			
1)2)	Diagnosis	ICD10 Code	'C001', 'C003', ...according to the list, except for 'C220'
3)	Operative notes	ICDCM or surgical procedure	'509078', '509079', ... or surgical procedure= 'partial biliary tract resection'...
4)	Diagnosis	ICD-10 codeor diagnosis	'pleural effusion (refractory)' or 'refractory pleural effusion' and so on
5)	Diagnosis	ICD-10 code	'T781','T887'

Figure 1 An example of replacement of trial eligibility criteria with patient characteristics for comparisons with the electronic medical records (EMRs). The trial eligibility criteria, replaced patient characteristics and matched data elements of EMRs are presented in the first, second and third columns, respectively. HCC, hepatocellular carcinoma; PS, performance status; TAE, transcatheter arterial embolization; TAI, transcatheter arterial infusion chemotherapy.

were able to predict prior to the start of a trial whether the trial would have a low enrollment because of fewer than expected eligible patients. If researchers are able to accurately predict a shortage of eligible patients, they may modify the eligibility criteria, recruit more participating institutions or abandon the trial to avoid wasting funds and efforts as well as exposing patients to unnecessary risk.

A number of screening methods for EMRs for eligible patients have been developed [7,8,10,11,18-20]. The search method for eligible patients used in our study was based on the patient treatment information rather than the plain text description of the disease in the EMRs. Although we may underestimate the number of potentially eligible patients who were diagnosed with the target disease without standard therapy, we consider those patients to be patients without active disease, patients who are unable to be treated or patients who are unwilling to be treated. Thus, there is little chance to enroll these patients into a clinical trial. When there is no standard therapy for the target disease or the target

stage of the disease, one must review the text in the EMRs manually or incorporate an adequate text mining technology to improve the search precision. However, we speculated that the combination of a diagnosis with other information may help refine the estimation [23], and we found that the EMR data and the estimation of the number of patients were accurate enough to predict some of the low enrollment trials.

Approximately one-half of all patient characteristics replaced from the trial eligibility criteria were matched with data elements in EMRs. Considering that the degree of matching in total or by category was not inferior to that achieved in a previous study [21], the included 19 trials are not biased, despite their small number. However, 45% of the patient characteristics were not matched with data elements in the EMRs, which may lead to an overestimation or underestimation of the number of eligible patients in the EMRs. Some trial criteria, such as 'pregnant or lactating', 'measurable disease by RECIST' and 'New York Heart Association class I', were classified as 'Not applicable' and were not considered

Table 2 Degree of translation to the electronic medical record (EMR) data

	Patient characteristics	Data elements in EMRs	Degree of translation[a]	Previous study[b]
Health status	236	141	0.61	0.60
Disease, symptoms and signs	120	80	0.68	0.81
Pregnancy-related activity	12	0	0	0.16
Neoplasm status	24	16	0.67	0.75
Disease stage	10	1	0.10	0.25
Allergy	12	4	0.33	0.17
Organ or tissue status	54	40	0.75	0.74
Life expectancy	4	0	0	0
Treatment or healthcare	45	24	0.55	0.57
Pharmaceutical substance or drug	26	10	0.40	0.35
Therapy or surgery	19	14	0.74	0.74
Device	0	0	NA	0
Diagnostic or lab results	84	47	0.56	0.54
Diagnostic or lab results	84	47	0.56	0.54
Receptor status	0	0	NA	0
Demographics	21	21	1.00	0.85
Age	20	20	1.00	0.95
Special patient characteristic	0	0	NA	0.33
Literacy	0	0	NA	0
Gender	1	1	1.00	1.00
Address	0	0	NA	0
Ethnicity	0	0	NA	0
Ethical consideration	12	0	0	0.08
Consent	8	0	0	0.06
Enrollment in other studies	1	0	0	0
Capacity	2	0	0	0.16
Patient preference	1	0	0	0
Compliance with protocol	0	0	NA	0
Lifestyle choice	10		0.20	0.82
Addictive behavior	5	0	0	0.90
Bedtime	0	0	NA	0
Exercise	0	0	NA	0
Diet	5	2	0.40	0
No fitting category	17	0	0	-
Total	425	235	0.55	0.55

[a]The degree of translation = the number of patient characteristics/the number of data elements in EMRs.
[b]Previous study: the fraction of documentable patient characteristics in previous study [21]. The authors calculated the fraction of patients with any data in at least one corresponding data element for each patient characteristic.

when determining whether the patient should be excluded. In addition, the diagnosis in the EMRs does not necessarily reflect the current condition of the patient. Temporary diagnoses or diagnoses related to the payment of medical insurance are often included in the EMRs and provide false or misleading information that leads to overestimating the number of eligible patients in the EMRs. However, because the exclusion of three trials with low levels of matching did not change the result of the correlation analysis or the ROC analysis, the impact of low levels of matching did not seem to be substantial.

In addition, the eligible EMR patient index is necessary but not sufficient to predict low levels of recruitment. Disappointingly, approximately half (four of ten) of the trials with an eligible EMR patients index greater than 1.7 resulted in low enrollment in this study. This finding

Figure 2 Correlation between the eligible electronic medical record (EMR) patient index and the accrual achievement in 19 trials. The eligible EMR patient index = the number of eligible patients identified from the EMRs per year/target sample size per year. The accrual achievement = the number of enrolled patients per year/target sample size per year.

Figure 4 A plot of the number of searched eligible patients both in the year preceding and the year following the opening of a trial.

results from the index not considering the willingness of patients and from the inaccuracy of EMR data. For instance, only 51% of the eligible patients agreed to participate in a cancer trial at one university-based cancer center [24]. Indeed, the consent rates in the trials conducted in our center ranged from 25% to 100% (data not shown). Four times as many patients as the number of eligible patients in EMRs are necessary when the consent rate of the trial is 25%. Therefore, investigators should consider other disincentive factors that would

Figure 3 The receiver operating characteristic (ROC) analysis of the eligible electronic medical record (EMR) patient index in 19 trials.

empirically influence a patient's consent, such as foreseeable risks or inconveniences to the patients, and the investigators can then determine whether the trial would in fact achieve its target sample size.
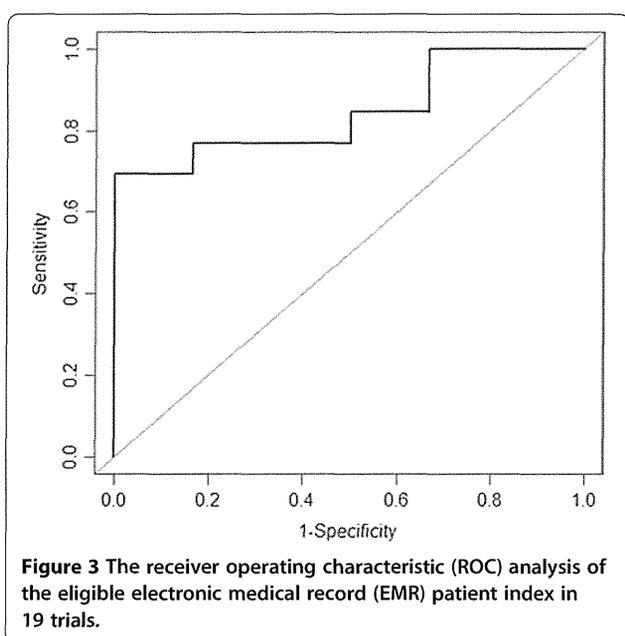
Our method also excluded a manual review of the EMRs. In previous studies, the eligible patients were generally identified by the EMRs in two steps: (1) the patient characteristics were screened and matched with standardized codes (for example, ICD codes) or numeric data; and (2) the medical records were manually reconfirmed by the medical staff [10,11]. Our aim was to obtain the total number of eligible patients instead of examining whether an individual patient was eligible for the trial. Therefore, we did not confirm whether the patients searched by the EMR retrieval system were eligible for the trial by verifying the entirety of their EMR data. As a result, the privacy of patients who had not given consent to participate in the trial is protected, while investigators can still speculate on the feasibility of the trial protocol.

The estimated number of eligible patients during the year of the trial accrual period did not exhibit a substantial increase compared to that of the preceding year. Researchers were unable to enroll more patients than they routinely cared for, regardless of the intensity of the recruitment efforts. The acquisition of new patients may be difficult because of the high degree of development among medical institutions and the guaranteed access by Japanese patients to any institution under the comprehensive medical insurance system. Additionally, most patients in Japan would have already been diagnosed or treated by specialists in a branch of medicine [25].

One limitation of this study was that the process of 'replacement' was not the exact translation of the trial eligibility criteria into data elements in the EMRs and instead depended on physicians' conception or the information presented in the trial protocol; thus, disagreement concerning the replacement or incomplete replacement may occur. Another limitation is that the eligible EMR patient index cannot predict all trials that will result in a failure of accrual (sensitivity, 0.645). The index is designed for a single institution and for a relatively small number of target trials. The cut-off value of the eligible EMR patient index in another institution may be different from ours. To speculate whether there are enough potentially eligible patients at a participating trial site for a multicenter clinical trial, each site must be equipped with an efficient EMR retrieval system. Moreover, this study was exploratory in nature, and prospective studies would be needed to validate the predictive ability of the eligible EMR patient index for future clinical trials.

Conclusions

Our study suggests that in addition to the knowledge of experienced investigators, the health information in EMRs could be a useful component of the feasibility study when planning a clinical trial. Establishing a step to check whether there are likely to be a sufficient number of eligible patients enables sponsors and investigators to concentrate their resources and efforts on more achievable trials.

Abbreviations

AUC: Area under the curve; EMRs: Electronic medical records; KUH: Kyoto University Hospital; ROC: Receiver operating characteristic; UMIN-CTR: University Hospital Medical Information Network Clinical Trial Registry.

Competing interests

All authors declare that they have no competing interests.

Authors' contributions

ES designed the study, replaced the trial eligibility criteria with the EMR data, collected data and wrote the manuscript. KY designed the study, developed the ERS system, wrote computer programs and collected data. ST designed the study and conducted the statistical analysis. MS and KY replaced the trial eligibility criteria with the EMR data. MY is the owner of the ERS systems and supervised the study. All authors read and approved the final manuscript.

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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

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 "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] 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] 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" "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" 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" 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] 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] 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 "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,