Off-Label Use of Rituximab in a Multipayer Insurance System

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Abstract

Purpose: Off-label prescribing in oncology is common and unregulated. The aim of this study was to describe the off-label use of rituximab, a novel anti-CD20 antibody, among patients from a large proprietary insurance database to understand how frequently and appropriately off-label prescribing occurs for this medication.

Patients and Methods: In this descriptive study, 11,232,642 patients were enrolled in the D2 Hawkeye commercial insurance database between 2001 and 2007, and 2,782 patients received rituximab. The main outcome measures were quantity and type of off-label usage, and expenditures for off-label usage.

Results: Seven hundred five (25.3%) patients received rituximab for off-label indications, and of those, 332 (47.1%) received rituximab for uncertain or inadequate evidence–based diagnoses. Expenditures for off-label indications were 17.1% of expenditures for rituximab usage.

Conclusion: The frequent use of rituximab for off-label indications should lead to improved postapproval surveillance of biologics by the US Food and Drug Administration, so that use can be adequately studied. This will also facilitate improved regulatory mechanisms to ensure evidence-based use.

Introduction

The Food and Drug Administration (FDA) spends more time and money on initial drug approval than it does on postapproval surveillance of medication usage.[1] Physician survey studies suggest that off-label medication prescribing is common, totaling 21% of overall use among frequently used drugs.[2,3] Off-label usage in oncology is thought to be common and is defined as the use of medications for different types of cancer or for different doses or durations of treatment than were described in the FDA approval process, or as part of a nonapproved chemotherapy combination.[4] However, little is known about whether novel biologic agents, now widely used in oncology and other specialties, are administered within the range of evidence-based practices.

In 1997, rituximab became the first monoclonal antibody approved by the FDA, initially for the treatment of relapsed or refractory, low-grade (indolent) or follicular, CD20-positive non-Hodgkin's lymphoma.[5] Since then, FDA indications for rituximab have broadened to include other B-cell lymphomas, initial treatment for previously specified types of non-Hodgkin's lymphoma, and rheumatoid arthritis.[6] Kocs et al found that 75% of rituximab prescriptions at a single academic institution were considered to be for off-label use, whereas a similar study revealed only 28 off-label uses in a tertiary hospital over a 3-year period.[7,8] As a new, nongeneric medication, rituximab is expensive, and understanding how it is used in practice may help shape health care policy and reimbursement strategies. The purpose of this study was to describe rituximab use in the general population among a broad range of institutions and geographical locations in a multipayer insurance system to better define off-label usage.

Patients and Methods

This is a descriptive study that used a comprehensive sample of commercially insured patients in all 50 states, Puerto Rico, and the U.S. Virgin Islands contained within the D2-Hawkeye proprietary database. This medical claims database is a privately held compilation of nationwide insurance companies that contains patient-level data sets with pharmaceutical and diagnostic information.

The database was queried by using the rituximab J-code, returning data for every accessible patient who received rituximab between 2001 and 2007. Each rituximab administration was linked to an International Classification of Diseases, Ninth Edition (ICD-9) code associated with that usage. In addition, information on a patient's age and sex was provided. For patients who received rituximab between 2005 and 2007, information regarding the total amount reimbursed for the rituximab claim was also obtained.

All attempts were made to identify a disease-specific ICD-9 code for each patient. Rituximab administrations were stratified as on-label or off-label on the basis of the 2009 FDA specifications. The nonspecific ICD-9 codes Lymphomas and Diffuse Disease of Connective Tissue were presumed to be for the on-label indications of non-Hodgkin's lymphoma and rheumatoid arthritis, respectively, if a more specific diagnosis was unobtainable. It was also assumed that rituximab was given as part of a specific protocol for the on-label indications at acceptable doses with appropriate additional chemotherapeutic agents.

If rituximab use was linked to a nonspecific ICD-9 code, the database was queried for that patient's entire list of claims linked to ICD-9 codes. The ICD-9 coding system allows for one degree of specificity in pathologic subtyping beyond the Lymphomas code category. If a more specific diagnosis (ie,

Nodular Lymphoma rather than Lymphomas) was present anywhere in the patient's list of ICD-9 indications, the rituximab-linked diagnosis was changed and noted. If an administration was linked to a nondisease or nonsensical ICD-9 code (eg, "Routine gynecological exam," "Dizziness and giddiness") and a disease-specific diagnosis was evident in the patient's list of claims linked to ICD-9 codes, the disease-specific ICD-9 item was used.

Off-label rituximab administrations linked to a diagnosis were stratified by means of the Stafford methodology for off-label prescribing analysis using the Drugdex compendium.[2] Drugdex evaluates medication usage on the basis of three quality-oriented criteria, and three ordinal levels were used for off-label indications (evidence-based, uncertain, and inadequate evidence) on the basis of the Drugdex assessment (see Table 1).

For diagnoses not commented on by Drugdex, a PubMed literature search was done to collect available clinical trial data, and expert consultation was obtained. These diagnoses included multiple sclerosis[9] and juvenile rheumatoid arthritis.[10] On the basis of these data, the diagnosis was scored using the ordinal levels described above. Descriptive statistical analysis was performed using Microsoft Excel 2003 for calculation of means, medians, and percentages, and STATA 10.0 for diagnosis frequency analysis.

Table 1. Definitions and Stratifications

Drugdex Scoring Criteria
Efficacy: effective, evidence favors efficacy, evidence is inconclusive, ineffective
Strength of recommendation: class I (recommended), class IIa (recommended in most cases), class IIb (recommended in some cases), class III (not recommended)
Strength of evidence: grade A (good RCT evidence), grade B (less consistent RCT evidence), grade C (non-RCT forms of evidence)
Off-Label Stratification Definitions
Evidence-based off-label use: efficacy is effective or favors efficacy, evidence is A or B, and recommendation is I or IIa
Uncertain evidence base for off-label use: evidence A or B, and class IIb
Inadequate evidence for off-label use: efficacy is inconclusive or ineffective, evidence is C, or recommendation is III

Abbreviation: RCT, randomized clinical trial.

Results

Between 2001 and 2007, 11,232,642 patients were enrolled in the D2 Hawkeye database. Of these, 2,782 patients received rituximab at least once, had an ICD-9 code recorded, and were included in our study. On-label indications accounted for 2,077 (74.7%) administrations, and 705 (25.3%) administrations were for off-label indications (Table 2). Among off-label indications, 373 (52.9%) uses were for evidence-based diagnoses, and 332 (47.1%) administrations were for either uncertain or inadequate evidence–based diagnoses. The mean and median ages of patients who received off-label, evidence-based diagnoses were 65 and 64 years, respectively, whereas those of patients with uncertain and inadequate evidence–based diagnoses were approximately 10 years younger.

For off-label usage stratification, only chronic lymphocytic leukemia (CLL) met the standard of being an evidence-based indication per the Drugdex criteria, and this diagnosis represented 373 (52.9%) patients. Among 246 (8.8%) uncertain evidence–based diagnoses, 140 (56.9%) were for thrombocytopenias assumed to be immune thrombocytopenia purpura (ITP), 45 (18.3%) were for Waldenstrom's macroglobulinemia, and 23 (9.3%) were for autoimmune hemolytic anemia (Fig 1). Of the 86 (3.1%) inadequate evidence–based administrations, 11 (12.8%) patients received rituximab for Hodgkin's disease, nine (10.5%) for hairy cell leukemia, and six (7.0%) for breast cancer. Twenty (23.3%) patients who received inadequate evidence–based diagnoses were considered as having Other Diagnoses, reflecting inappropriate ICD-9 diagnoses without suitable replacements.

Financial information for 2005 to 2007 demonstrated that $9,027,143 was spent on off-label rituximab use, representing 17.1% of all rituximab reimbursements (Table 2). The amount spent on off-label uncertain or inadequate evidence–based diagnoses was $3,989,851, which represented 7.6% of all rituximab expenditures.

Table 2. On-Label and Off-Label Descriptive and Financial Data

							Off-Label Levels					
	Total		On-Label		Off-Label		Evidence-Based		Uncertain		Inadequate	
Characteristic	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
No. of patients	2,782	100	2,077	74.7	705	25.3	373	13.4	246	8.8	86	3.1
% of off-label		NA		NA		100		52.9		34.9		12.2
Age at first dose, years												
Mean	60		61		60		65		54		55	
Median	61		61		61		64		56		57	
Male	1,444	51.9	1,068	51.4	375	53.2	230	61.7	112	45.5	34	39.5
Total expenditures (US dollars)*	52,708,083		43,680,940		9,027,143		5,037,291		3,296,943		692,909	
% of total expenditures*		100.0		82.9		17.1		9.6		6.3		1.3

Abbreviation: NA, not applicable.
*2005-2007 only.

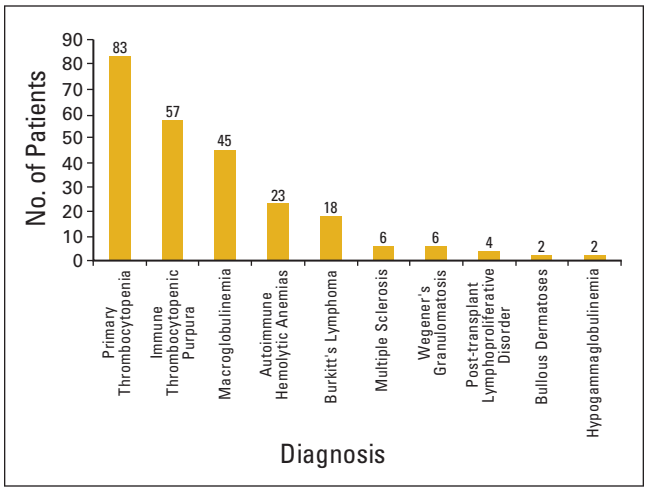

Figure 1. Off-label uncertain evidence–based diagnoses.

Discussion

To our knowledge, this is the largest examination of off-label rituximab usage and the first to assess usage patterns in community settings spanning a large geographical region. Although the overall percentage of off-label usage was smaller than those in earlier single-institution studies, 47.1% of off-label administrations were for diagnoses that carried uncertain or inadequate levels of evidence for use. In certain cases, rituximab was used for diagnoses for which there are no data to support its use, although individual clinical circumstances may have supported a trial. We are in favor of postmarketing surveillance mechanisms to ensure that such usages are evaluated for effectiveness, so that novel medications are used primarily for evidence-based indications.

Furthermore, although rituximab expenditure represents a small segment of the overall health care costs across the country, we feel it has real implications for the health care system on a population basis. Given that 17.1% of community rituximab expenditures were for off-label indications, it would also be financially logical to call for more robust funding and support of postapproval FDA monitoring, or mandatory third-party registration of biologic therapy usages, to ensure evidence-based usage of novel therapies and avoid inappropriate health care spending.

The February 2010 FDA decision to consider CLL an on-label indication does not apply to the usage period of this study, but reassessing the data with this change would result in 100% of off-label usage for the uncertain or inadequate evidence categories. Interestingly, the start year for this database (2001) coincided with the publication of early trials using rituximab for CLL,[11] demonstrating a rational example of off-label usage. Similarly, many of the diagnoses stratified to the uncertain category are often accepted as clinically appropriate, reflecting a lack of randomized controlled trials demonstrating efficacy. This was notable for ITP, Waldenstrom's macroglobulinemia, and autoimmune hypolytic anemia, among other diagnoses. Although there are concerns about the accuracy of drug compendia generally,[12] the Drugdex compendium has been used successfully in previous studies.[2]

This study was limited by the lack of specificity in ICD-9 coding; the largest diagnostic code was Lymphomas, a broad entity that is presumed but not confirmed to reflect B-cell non-Hodgkin's lymphoma. We addressed this by assuming that the Lymphomas group was evidence based to provide the most conservative estimate of off-label use. In addition, we acknowledge that there is evidence for the use of rituximab in lymphocyte-predominant Hodgkin's disease,[13] and an unknown number of cases classified as Hodkgin's disease may be in that category, but ICD-9 coding does not allow for this degree of specificity.

It was also not possible to determine whether rituximab was coadministered appropriately with other agents, which would likely have increase off-label use. It is unknown how many diagnoses were coded in error, and although every effort was made to extract the most specific and likely diagnosis, we were unable to review patient charts to confirm our results. In accepting these limitations to ICD-9 coding, we acknowledge that the reported data reflect a best-case scenario and that the true percentage of off-label use is likely to be significantly higher.

We suspect many patients categorized as having received Other Diagnoses were coded in error, as their linked codes included "Disease of Nail" and "Acute Otitis Media." However, this group represented 2.8% of off-label usage and likely would not significantly affect the findings were they reassigned to other categories on the basis of their actual diagnoses.

In sum, rituximab is frequently being used in practice for off-label diagnoses, and many usages are not supported by uniformly accepted levels of evidence. As more scrutiny is placed on off-label prescription regulation,[14,15] it is important to examine population-wide medication use to document what is currently considered standard prescription practice and to analyze what proportion of such use is supported by scientific evidence. It would be worthwhile to compare these usage patterns with those in a single-payer system, such as Veterans Affairs, staff model HMO systems, or Medicare to determine whether a particular system is more effective at monitoring off-label usage and limiting it to diagnoses with sufficient evidence in the postapproval setting.

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Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author

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