Review

The Case for Real-world Evidence in the Future of Clinical Research on Chronic Myeloid Leukemia

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ABSTRACT

Purpose: In light of recently published guidelines from the US Food and Drug Administration (FDA) on the communication of real-world data (RWD) and real-world evidence (RWE) to support regulatory decision making, it is important to understand how such data are developed, the limitations of these data, and how to best use RWD to improve patient care. Historically, the use of RWE has been approached with skepticism because of its often-retrospective nature compared with data from conventional randomized controlled trials (RCTs). This review discusses the role and function of RWE and RWD in clinical research. We summarize the types of RWE used in clinical research, outline the challenges and limitations involved with these data, and suggest how these types of analyses can supplement results from clinical trials to foster a more complete understanding of a drug or disease area of interest. In particular, we focus on the role of RWE in investigating chronic myeloid leukemia (CML) and tyrosine kinase inhibitor therapy for CML.

Methods: We reviewed FDA guidance on the use of RWE and conducted a PubMed literature search to evaluate published data from real-world studies in CML.

Findings: RWE includes analysis of RWD gathered from nonconventional sources, including patient registries, observational studies, and social media, among others. Importantly, although real-world studies do not adhere to the same degree of controlled conditions and predefined patient-management strategies as do conventional clinical trials, analyses resulting from these studies can be held to a high degree of validation and standardization, making them as meaningful as those from RCTs. In CML, RWE has informed early treatment milestones and has provided a window into patient perspectives regarding treatment. These types of analyses have already informed and can continue to inform disease management. These improvements in disease management, in turn, will help clinicians to better forecast treatment challenges and allow for the optimization of future treatment paradigms.

Implications: Real-world studies are different from conventional RCTs and therefore provide insight into distinct aspects of treatment and patient outcomes. Together with results from clinical trials, RWE can help to illustrate a more complete picture of the tolerability, effectiveness, and impact of a drug. The recently published guidelines indicate that the FDA expects a growing role for RWE. (*Clin Ther*. 2019;41:336–349) © 2019 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Key words: chronic myeloid leukemia, patient outcomes, real-world data, real-world evidence.

INTRODUCTION

Conventional *randomized controlled trials* (RCTs) are rigorous scientific examinations of the tolerability and efficacy of potential new therapies.[1] RCTs define precise clinical end points, maximize adherence, minimize variance of clinical conditions, and are limited to relatively homogeneous patient populations through

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strict eligibility criteria and controlled conditions.[2,3] During RCTs, patients are managed according to study-defined protocols and typically undergo more intensive monitoring than in routine practice, with more detailed collection and recording of data than is typical in ordinary medical records.[1] In addition, randomization in RCTs aims to minimize bias by balancing patient characteristics between treatment groups and thereby maximizes the likelihood that any observed differences result from differences in assigned study treatments.[1,3] Although RCTs can provide crucial information on the tolerability and efficacy of a treatment, certain aspects of RCTs limit the applicability of their results to all patients.[1–3] RCTs typically comprise patient populations that are relatively homogenous and not identical to patient populations outside of RCTs.[1–3] The use of large-scale, highly selected patient populations in RCTs creates high statistical power, which can lead to the detection of statistically significant but small differences in patient outcomes.[3] Patient education and tightly controlled treatment administration are standard in many RCTs and may result in higher rates of treatment adherence and, therefore, improved response rates compared with those in routine clinical practice.[1,2,4]

Real-world data (RWD) are data regarding patient health status and health care delivery that are routinely collected from a variety of sources, including patient registries, databases, clinical case reports, claims and billing reports, medical devices, and electronic health records; RWD are analyzed in accordance with high-quality research methods and can be valuable for complementing the information obtained from conventional clinical trials.[1,5] In addition, social media as well as electronic devices and apps that continuously monitor patient biometrics are massive data sources that can be used for epidemiologic purposes.[1] Results from certain types of clinical trials (those with less stringent enrollment criteria and patient-management guidelines than in conventional RCTs) can also be considered RWD.[6] *Real-world evidence* (RWE) is clinical evidence derived from the analysis of RWD regarding the use, as well as the benefits and risks associated with the use, of a medical product.[1,5] Importantly, RWE is not anecdotal but requires validation and standardization of data.[7]

RWD may uncover aspects of disease management that could be optimized to improve patient care.[2] Analysis and interpretation of RWD may also help to guide the development of improved health plan operations, health system administration, patient or provider communications, cost management, and epidemiologic research. RWD can also contribute to the design of more efficient RCTs.[7] In the chronic myeloid leukemia (CML) field, RWE can potentially contribute substantially to the understanding and optimization of real-life treatment patterns and patient outcomes. RWE can reveal insights into patient quality of life, the actual frequency of disease monitoring in clinical practice, factors that contribute to treatment intolerance or discontinuation, factors that determine treatment choice, patterns of treatment switching and associated outcomes, and health care resource utilization and costs.[2,8–11] Results from RWE studies, as well as those from RCTs, must be interpreted with consideration of their limitations,[3] and the quality of RWD should be assessed according to the specific clinical or regulatory context that the data are intended to serve.[7]

MATERIALS AND METHODS

In this analysis, the US Food and Drug Administration (FDA) guidance documents on the use of RWE in regulatory decision making (Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices: Guidance for Industry and FDA Staff[5] and Drug and Device Manufacturer Communications With Payors, Formulary Committees, and Similar Entities—Questions and Answers: Guidance for Industry and Review Staff[12]) were reviewed. To identify studies using RWD and RWE in CML, a PubMed literature search was conducted using search terms including 'chronic myeloid leukemia' AND ('real-world' OR 'registry'). Recent congress abstracts reporting the results from real-world analyses were also reviewed. Representative publications were selected for inclusion in this review. No predefined criteria were established to select publications; rather, publications were selected that would allow for the presentation of a broad summary of the use of RWD and RWE in the CML field.

RESULTS

FDA Guidance on RWE

The FDA has issued guidance documents on the use of RWE to support regulatory decision making with regard to medical devices and on the communication of certain types of RWD (namely, health care economic

information) between manufacturers and payers and formulary committees.[5,12] Additionally, contributors from several offices within the FDA published an editorial article in *The New England Journal of Medicine* in 2016 discussing RWE and its place in medical research.[1] The specific recommendations in the FDA guidance document on the use of RWE in regulatory decision making focus on medical devices; however, the definitions and characteristics of valid RWD included in this guidance are relevant to research on pharmaceutical approaches as well.[13] The FDA states that RWE can support and inform conclusions on the performance of medical products if the RWD that generate RWE meet certain evidentiary standards. The FDA notes that potential sources of RWD are to be selected based on the ability of these sources to address a specific question, and the FDA emphasizes the importance of ensuring accuracy, relevance, and reliability when evaluating RWD.[5] In its guidance on communication of health care economic information, the FDA carefully outlines the information about a study that must be communicated to ensure understanding and appropriate interpretation of the results; the study information includes background and contextual information as well as clear and prominent explanations of the study design and methodology (eg, type of analysis, patient population, time horizon, and assumptions), generalizability, limitations, associated sensitivity analyses, and other supporting information.[12]

Types of RWE Studies

RWE studies can be prospective (eg, observational reports from patient registries or pragmatic trials) or retrospective (eg, analyses of claims databases or medical records).[5] *Prospective observational studies* using data from patient registries offer a mechanism to follow up on a large cohort of patients and collect information on outcomes of interest over time.[14] *Patient registries* can be used to address several research questions by prospectively collecting information on many topics, such as compliance, patient experience, the frequency of rare events, health care access, and outcomes among heterogeneous patient populations.[15] Some prospective clinical trials can also be considered RWE studies.[6] These clinical trials, sometimes referred to as *pragmatic trials,* are distinct from conventional RCTs in that they typically have less stringent enrollment criteria and on-study management protocols. As a result, they are expected to better reflect routine clinical practice.[6]

Retrospective cohort analyses use previously recorded information from insurance claims databases or patient medical records to analyze outcomes in a patient cohort of interest or to compare outcomes among cohorts.[1,16–19] One type of retrospective cohort analysis is a *retrospective claims database study,* in which data on treatments and outcomes are gathered from billing codes submitted to payers; these databases can be a robust, expedient, and inexpensive source of data.[16] Analyses of patient medical records, including electronic health records, can capture data on management practices.[19] Medical records contain information such as symptoms and impact of various treatment strategies and provide clinical or operational data that can guide future clinical practice and reveal epidemiologic trends.[19] Longitudinal studies of medical records enable the evaluation of patient variables that may not be included in RCTs.[19] Another source of RWD is patient surveys, which are designed to assess patient experiences or opinions.[20,21]

Role of RWE

Data Gaps Not Addressed in RCTs

RWE can provide insights not readily attainable from RCTs (Table I).[1–3] Specific patient populations, such as elderly patients, pregnant patients, or patients with specific comorbidities, are often excluded from clinical trials.[3,49,50] RWE studies can provide insight into the outcomes of patient populations that may be underrepresented in RCTs.[51–54] These analyses are important supplements to the data obtained in conventional RCTs; for example, patients with comorbidities may experience greater toxicity in clinical practice than is observed in trials.[3] Most RCTs focus on therapeutic efficacy and short-term toxicity; long-term tolerability and patient-centered outcomes, such as quality of life, may not be fully captured.[2,3] In contrast, longer study durations and large-scale databases used in RWE studies can reveal rare adverse events (AEs), assess the true incidence and impact of AEs in routine clinical practice, and monitor AEs that emerge after long-term treatment; they can also be a valuable source of information on patient-centered outcomes.[2,55] Small differences in

Table I. Contributions of conventional clinical trials and real-world evidence (RWE) to end points used generally in research and specifically in chronic myeloid leukemia (CML).

End Point	Clinical Trials	RWE
Research studies		
Response	Short-term treatment effects[22] Impact on risk for developing a condition or disease complication[23] Impact on disease symptoms[24] Response rate at discrete time points[22,25,26]	Long-term treatment effects[27] Impact on risk for developing a condition or disease complication over time[28] Outcomes in patients not typically included in RCTs[29,30] Response rates in clinical practice[31] Real-world disease-management practices[31]
Survival	OS at discrete time points[22,25,26] Reported causes of death[25]	Long-term survival[32,33] Survival in patients not typically included in RCTs[30]
QOL	QOL at start of analysis and discrete short-term time points[34–37]	QOL[38]
Tolerability	Detailed data on adverse events occurring early during treatment[22] Treatment discontinuation[22,25,26]	Long-term treatment side effects and complications[39]
CML research studies		
Response	Molecular, cytogenetic, and hematologic response rates at discrete time points[22,25,26] Kinetics of reduction in *BCR-ABL1* transcript levels[40] Assessment of whether a patient meets designated treatment response landmarks (eg, target response levels at 3, 6, and 12 months from the start of treatment)[40] Rates of CML progression at early time points[40] Development of evidence supporting new treatment practices, such as criteria for attempting treatment-free remission[34,41–47]	Long-term treatment effects[27] Long-term rates of CML progression[32] Rates of treatment failure in clinical practice[14,30] Analysis of treatment switching patterns, including rates of treatment switch due to treatment failure[14,30] Analysis of treatment-free remission practices and outcomes in clinical practice[48] Outcomes in patients not typically included in RCTs[29,30] Response rates in clinical practice[31] Real-world disease management practices[31]
Survival	OS at discrete time points[22,25,26] Reported causes of death[25]	Long-term survival[32,33] Long-term rate of CML-related deaths[33] Survival in patients not typically included in RCTs[30]
QOL	QOL at start of analysis and discrete short-term time points[34–37]	QOL[38]
Tolerability	Detailed data on adverse events occurring early during treatment[22] Treatment discontinuation[22,25,26]	Long-term treatment side effects and complications[39]

OS, overall survival; QOL, quality of life; RCT, randomized controlled trial; RWE, real-world evidence.

response rates or survival that are evident in a large-scale RCT may not be observed in routine practice with a less homogeneous patient population.[3] RWE studies can follow RCTs to report on patterns of patient management, toxicity, and treatment outcomes in routine clinical practice; assess how outcomes evolve in a real-world setting; and determine whether clinical practice changed as a result of the study's findings.[2,3,55] RWE can also be used to evaluate the cost-effectiveness of available treatments.[2]

Weaknesses and Challenges Associated With RWE

Observational studies are important in epidemiologic investigations and surveillance; however, when treatment effects are assessed, it is difficult to conclusively determine whether any observed differences were due to the treatment rather than confounding factors.[1] Because of their relatively flexible study designs and heterogeneous patient populations, RWE studies may not detect small differences between treatment groups.[2] A nonrandomized design limits the internal validity of RWD and increases the risk for bias, which may increase the risk for generating unreliable conclusions.[3,55] Observational studies are associated with an increased risk for incomplete datasets, which complicate statistical analysis.[2] Many RWD sources are not designed for research purposes; therefore, the accuracy and reliability of data collected from these sources may be unknown.[1] Researchers must be clear about how RWE can be used most effectively; RWE studies are intended to complement, not compete with or replace, RCTs.[1,55]

RWE Studies in CML

CML accounts for ~15% of all cases of leukemia in adults.[41] The disease is characterized by 3 phases: chronic phase, accelerated phase, and blast crisis. The treatment landscape in patients with CML changed after the approval of imatinib, a tyrosine kinase inhibitor (TKI), in 2001.[50] Since then, several newer TKIs have also been approved, and TKI therapy is now the recommended treatment for patients with CML.[41] Due to the substantial efficacy of TKI therapy, life expectancy in patients with CML now approaches that of the general population.[56] The management of TKI therapy over time and the possibility of permanently stopping therapy have been, and are still, topics of much investigation.

There are several areas in which RWE can contribute to the understanding and optimization of CML-management practices. Many RWE studies have informed early treatment milestones in CML. An RWE study in 483 patients (median age, 48 years) with newly diagnosed CML treated with first-line TKIs showed that 3-month *BCR-ABL1* level significantly predicted 3-year event-free survival (EFS); 3-year EFS rates based on *BCR-ABL1* transcript levels on the International Scale (IS) at 3 months were 95% if $BCR\text{-}ABL1^{IS}$ was $\leq$1%, 98% if $BCR\text{-}ABL1^{IS}$ was >1% to 10%, and 61% if $BCR\text{-}ABL1^{IS}$ was >10%.[57] A similar result was seen in a study in 282 patients (median age, 46 years; female, 44.3%) treated with imatinib as first-line therapy, which showed that of *BCR-ABL1* transcript levels at 3, 6, and 12 months, the transcript level at 3 months was the most strongly predictive of progression-free survival, overall survival, and complete molecular response; additionally, at 6 and 12 months, *BCR-ABL1* transcript levels were more predictive of outcomes than were cytogenetic responses.[58]

RWE studies can also be useful for helping to better understand the actual patterns of TKI use and CML management in clinical practice, as well as patient perspectives on their disease and treatment. One example of such a study is SIMPLICITY (Studying Interventions for Managing Patients With Chronic Myeloid Leukemia (CML) in Chronic Phase: The 5-Year Prospective Cohort Study), an observational study in 1242 patients (median age, 57 years; female, 45.3%) with CML treated with imatinib, nilotinib, or dasatinib as front-line therapy.[9] SIMPLICITY was designed to assess patterns of TKI use, resource utilization, and patient-reported outcomes such as quality of life and patient satisfaction in routine clinical practice.[9,59] Early results from this study have suggested that disease-monitoring practices are rarely as rigorous as those recommended by the National Comprehensive Cancer Network or European LeukemiaNet and that many factors influence monitoring, such as where the patient is treated (Europe vs United States), type of practice (community vs academic), patient age (<65 vs $\geq$65 years), and whether the patient is receiving first- or second-line therapy.[9]

Another example of an informative RWE study is the EUTOS (European Treatment Outcome Study)

registry (N = 2904),[60] which was created to gain a better understanding of patient treatment and outcome patterns in clinical practice. For the EUTOS registry, baseline, treatment, and outcomes data were collected from the records of all adult patients (no exclusion criteria; median age, 55 years; female, 46%) with newly diagnosed CML across several European countries.[14,60] One outcome in EUTOS was the development of the EUTOS prognostic score, a novel method of predicting a patient's likelihood of achieving a complete cytogenetic response and of identifying patients at a higher risk for progression and impaired survival based on patient baseline characteristics.[61,62] Because clinical trials generally enroll younger patients who are taking fewer medications, large-scale registries provide the opportunity to assess the impact of polypharmacy, and potentially specific drug–drug interactions, on CML outcomes. Notably, to this point, such studies have not shown polypharmacy to be a risk factor for poorer CML-related outcomes among elderly patients.[63]

Factors associated with the long-term burden of CML, including treatment satisfaction and adherence, and the impact of chronic AEs on quality of life can be informed by RWE studies.[2,38] The potential utility of RWE studies in this regard is highlighted by the development of the MD Anderson Symptom Inventory for CML, a questionnaire used for evaluating a patient's quality of life.[38] This questionnaire was developed based on interviews and surveys of multiple cohorts of patients and CML experts.[38] Interestingly, in 2 studies of patients stopping nilotinib treatment to attempt treatment-free remission (TFR), there was little change in quality of life following treatment discontinuation or treatment resumption, although pain/discomfort was notably more common after stopping treatment.[34,35]

TFR has recently emerged as a treatment goal in CML on the basis of several clinical trials demonstrating that some patients with sustained deep molecular responses on long-term TKI therapy could stop treatment without losing their response.[34,41–47] The feasibility of TFR has been reproducibly demonstrated in several clinical trials; however, all of these trials have used stringent eligibility criteria.[34,42,43,45–47,64] Thus, analyses of RWD on TFR are important for understanding how this new concept can be incorporated into routine clinical practice,[48,65] particularly following the addition, in the National Comprehensive Cancer Network guidelines on CML, of recommendations on the use of TFR in clinical practice, and the incorporation of TFR data into the labeling of nilotinib in the United States.[41,66] Notably, a survey of US physicians found that one-third reported having attempted TKI discontinuation prior to the availability of the National Comprehensive Cancer Network TFR guideline,[48] further demonstrating the need for analyzing real-world treatment and management patterns.

Long-term or late outcomes may not be captured during RCTs, whereas RWE studies can provide a picture of long-term outcomes with CML treatment.[2] For example, RWE studies may help to reveal whether the relative risk for short-term cardiovascular AEs reported in clinical trials[22,25,26] translates into a real risk for long-term cardiovascular toxicity in a wider population of patients with CML. One such retrospective RWE cohort study followed up 896 patients with CML (mean age at diagnosis, 58 years; female, 46%; 94.4% with documented TKI treatment) for a median of 4.2 years and compared the incidence of vascular events in these patients with the incidence of vascular events in age- and sex-matched patients in a control cohort.[67] Patients with CML had greater risks for both arterial and venous vascular events than did patients in the control population. Data from an analysis comparing different types of TKI therapy were limited due to too few events for meaningful statistical evaluation; however, Dahlén et al.[67] reported that patients treated with nilotinib or dasatinib had an increased rate of myocardial infarction events compared with patients who received imatinib. Another retrospective study examining RWD in 584 patients with CML treated with TKIs (median age at start of treatment, 49 years; female, 41%) reported that cardiovascular events occurred in 53% of patients, and the highest risk ratio for the incidence of treatment-emergent cardiovascular and arteriothrombotic AEs was in patients who received second- or third-generation TKIs rather than imatinib.[39] Notably, findings from a recent study suggest that cardiovascular disease–related mortality is lower among patients with CML who are treated with TKIs than among patients diagnosed in the pre-TKI era, raising the

possibility that TKIs may increase the incidence but not the severity of cardiovascular events. This study also demonstrated that African American patients with CML treated with TKIs have an increased risk for cardiovascular disease–related mortality compared with white patients ($P = .004$), suggesting that African Americans may represent a particularly vulnerable population requiring more careful monitoring for cardiovascular disease.[68]

RWE studies can also be used to evaluate the impact of treatment adherence on clinical outcomes. For example, a prospective, single-institution cohort analysis of data from 87 consecutive patients with CML treated with imatinib found that poor treatment adherence was significantly associated with a lower likelihood of achieving a complete molecular response ($P < .001$) and higher risk for loss of cytogenetic response ($P < .0001$) and treatment failure ($P < .0001$).[4,69] Additionally, a retrospective cohort analysis found that patients with a medication possession ratio (MPR) of ≥90%, considered a high level of adherence, had lower rates of progression to accelerated phase/blast crisis and mortality than did patients with an MPR of <90%.[32] Retrospective cohort analyses can be used to evaluate disease-management practices and the impact of these practices on patient outcomes.[8] For example, a retrospective claims analysis of data from 1431 patients with CML in the United States found that 16% had 4 molecular monitoring tests, the recommended number of tests,[41] during the first year after diagnosis, while the majority of patients had fewer tests.[8] Notably, patients with fewer tests had poorer treatment adherence ($P < .001$) and had higher health care resource utilization and costs overall, including a higher number of inpatient days ($P = .010$), although an increase of 1 molecular monitoring test was also associated with a 3.0% increase in outpatient service days ($P = .002$).[8] Most importantly, the frequency of testing has been linked to outcomes, whereby patients who underwent more testing had an improved progression-free survival ($P = .001$).[31] Similarly, in a retrospective study of data from 516 patients with CML in chronic phase in India who received imatinib free of cost, the impact of treatment adherence was investigated on the basis of whether patients attended regular clinic visits at which the drug was dispensed; results showed significantly worse 5-year EFS among nonadherent patients compared with that in adherent patients ($P = .011$).[27]

Pregnant patients have been excluded from TKI clinical trials due to concerns about the teratogenicity of TKIs as demonstrated in animal models.[50] Unfortunately, CML is a disease that affects women of reproductive age, and health care providers are often faced with questions about how to treat patients prior to and during pregnancy. A retrospective study of RWD examined data from 13 women who were diagnosed with CML during pregnancy and an additional 15 who conceived while receiving TKIs. Among the women who were diagnosed with CML during pregnancy, 10 successfully carried infants to term, and all but 1 had an adequate response to TKI treatment initiated within 1 month of delivery. The 15 women who conceived while receiving TKIs stopped treatment upon learning of their pregnancies, which led to 12 live births, including 2 infants with minor abnormalities (hypospadias and rotation of the small intestine). These patients remained off TKIs for a median of 10 months, during which time 40% lost their responses, but all subsequently achieved at least a complete cytogenetic response upon resuming TKI treatment. That study provided important information that clinicians can use to assure patients who are diagnosed with CML during pregnancy or who become pregnant while receiving a TKI.[29]

Vignette: RWE Analysis of Data From Elderly Patients With CML

To better understand how elderly Medicare beneficiaries with CML respond to second-line nilotinib or dasatinib therapy following initial treatment with imatinib, our group[30] conducted a retrospective cross-sectional cohort study of data from the US Centers for Medicare & Medicaid Services national administrative claims database. The analysis included patients with continuous Medicare Parts A, B, and D coverage, and data were sourced from the Medicare Research Identifiable Files (2006–2012). These files contain information on patient demographics as well as claims data relating to inpatient and outpatient care (from Medicare Part A), carrier and medical equipment files (from Medicare Part B), and therapeutic interventions (from Medicare Part D). The patient selection sample process is illustrated in Figure 1. Briefly, eligible

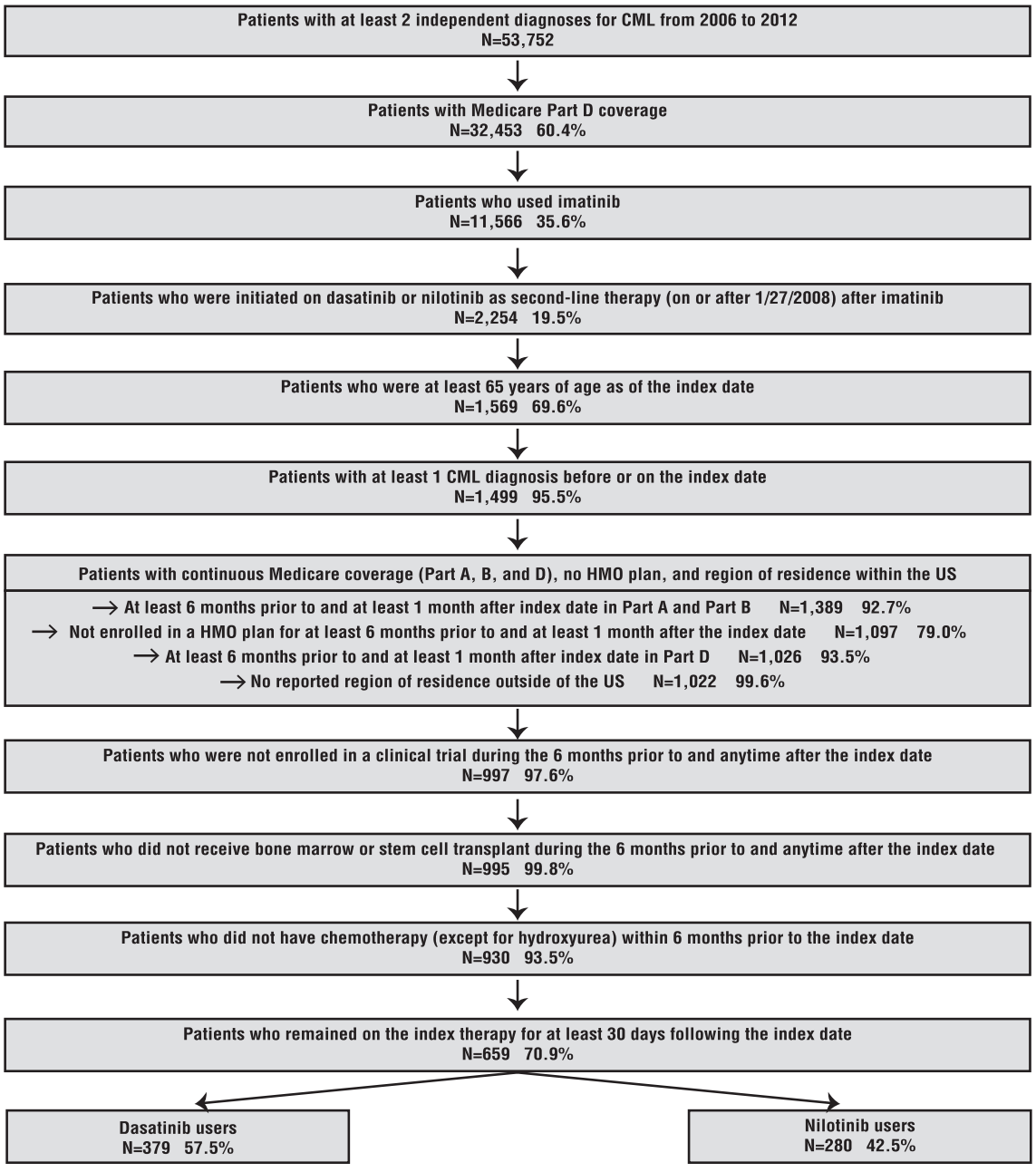

Figure 1. Patient selection sample process. CML, chronic myeloid leukemia; HMO, health maintenance organization. Reprinted by permission of Taylor & Francis Ltd.[30]

patients had ≥2 recorded CML diagnoses (*International Classification of Diseases, Ninth Revision—Clinical Modification* code 205.1×), were treated with front-line imatinib and second-line nilotinib or dasatinib, and were aged ≥65 years at the start of second-line therapy. Patients previously enrolled in a clinical trial or who received a stem cell transplant or chemotherapy other than hydroxyurea were excluded. A total of 379 dasatinib-treated patients and 280 nilotinib-treated patients were

Table II. Comparison of patient characteristics between the nilotinib and dasatinib cohorts[a].

Characteristic	Nilotinib (n = 280)	Dasatinib (n = 379)	P[b]
Mean age (SD), years[c]	76.25 (6.95)	75.36 (6.70)	.097
65–69 years, n (%)	57 (20.4)	82 (21.6)	.691
70–74 years, n (%)	69 (24.6)	123 (32.5)	.029[d]
75–79 years, n (%)	57 (20.4)	71 (18.7)	.603
80+ years, n (%)	97 (34.6)	103 (27.2)	.039[d]
Female, n (%)	177 (63.2)	232 (61.2)	.601
Region, n (%)			
South	131 (46.8)	167 (44.1)	.488
Northeast	47 (16.8)	68 (17.9)	.699
West	38 (13.6)	61 (16.1)	.370
Midwest	64 (22.9)	83 (21.9)	.770
Index year, n (%)			
2008	37 (13.2)	71 (18.7)	.058
2009	32 (11.4)	67 (17.7)	.026[d]
2010	82 (29.3)	91 (24.0)	.128
2011	70 (25.0)	84 (22.2)	.395
2012	59 (21.1)	66 (17.4)	.237
Mean observed duration of CML, days [median] (SD)[e]	866 [698] (648)	873 [786] (633)	.879
Mean imatinib duration prior to index date, days [median] (SD)[f]	801 [637] (632)	776 [666] (598)	.789
Mean length follow-up period, days [median] (SD)	702 [673] (420)	717 [665] (469)	.950
Follow-up period ≥6 months, n (%)	253 (90.4)	324 (85.5)	.061
Follow-up period ≥12 months, n (%)	204 (72.9)	276 (72.8)	.992
Follow-up period ≥18 months, n (%)	175 (62.5)	227 (59.9)	.498
Follow-up period ≥24 months, n (%)	128 (45.7)	173 (45.6)	.986
Adjusted disease complexity since CML diagnosis			
Mild	152 (54.3)	220 (58.0)	.336
Moderate	65 (23.2)	81 (21.4)	.573
Severe	63 (22.5)	78 (20.6)	.553
CML remission	37 (13.2)	44 (11.6)	.535
CML relapse	5 (1.8)	7 (1.8)	.954
Initiated the index TKI on the recommended dose, n (%)	149 (53.2)	281 (74.1)	<.001[d]
Quan-Charlson Comorbidity Index (CCI) score, excluding CML, mean (SD)[70]	1.40 (1.71)	1.21 (1.60)	.100
Quan-CCI score ≥1	164 (58.6)	196 (51.7)	.081
Quan-CCI score ≥2	99 (35.4)	120 (31.7)	.32
Quan-CCI score ≥3	63 (22.5)	69 (18.2)	.173
Comorbidities before the index date, n (%)[g]			
Anemia	125 (44.6)	167 (44.1)	.882
Chronic pulmonary disease	52 (18.6)	65 (17.2)	.637
Cardiovascular disease	108 (38.6)	109 (28.8)	.008[d]
Congestive heart failure	63 (22.5)	51 (13.5)	.002[d]

Table II. (*Continued*)

Characteristic	Nilotinib (n = 280)	Dasatinib (n = 379)	P[b]
Coagulopathy	27 (9.6)	29 (7.7)	.365
Depression	13 (4.6)	24 (6.3)	.352
Diabetes	86 (30.7)	109 (28.8)	.587
Fluid electrolyte disorders	48 (17.1)	56 (14.8)	.410
Hyperlipidemia	93 (33.2)	127 (33.5)	.937
Hypertension	156 (55.7)	219 (57.8)	.596
Hypothyroidism	39 (13.9)	52 (13.7)	.939
Macular degeneration	15 (5.4)	6 (1.6)	.006[d]
Neurological disorders	17 (6.1)	16 (4.2)	.282
Osteoporosis	13 (4.6)	29 (7.7)	.118
Peripheral vascular disease	23 (8.2)	31 (8.2)	.987
Pulmonary circulation disorder	14 (5.0)	8 (2.1)	.041[d]
QTc prolongation	36 (12.9)	35 (9.2)	.138
Renal failure	49 (17.5)	64 (16.9)	.836
Solid tumor	43 (15.4)	65 (17.2)	.539
Valvular disease	25 (8.9)	22 (5.8)	.123
Weight loss	16 (5.7)	17 (4.5)	.475

CML, chronic myeloid leukemia; TKI, tyrosine kinase inhibitor.
[a] Smith BD, et al. *Curr Med Res Opin*. 2016; 32(5):817–827, reprinted by permission of Taylor & Francis Ltd.
[b] *P* values were calculated using χ^2 tests for binary variables and Wilcoxon tests for continuous variables.
[c] Age was calculated as of the index date.
[d] Significant at the 5% level.
[e] Observed duration of CML was calculated between the first observed CML diagnosis and the index date.
[f] Observed duration of imatinib use was calculated between the first observed imatinib prescription and the index date.
[g] The list of comorbidities was based on Agency for Health care Research and Quality. Healthcare Cost and Utilization Project Elixhauser Comorbidity Software, version 3.7. https://www.hcup-us.ahrq.gov/toolssoftware/comorbidity/comorbidity.jsp. Accessed 18 August 2015.

identified for inclusion. The study period began when second-line TKI therapy was initiated (the index date) and ended at the date of the patient's death, the conclusion of continuous Medicare enrollment, or when data became unavailable. Outcomes in dasatinib- and nilotinib-treated patients were compared using multivariate regression models adjusted for potential confounding factors, including age, sex, region, Darkow CML complexity and Quan-Charlson Comorbidity Index[70] scores, and whether patients were initiated on TKI therapy at the recommended starting dose or at a different dose.

Results of this analysis revealed that the dasatinib-treated and nilotinib-treated cohorts had similar patient demographics and comorbidities (Table II[30]), although preexisting cardiovascular disease was more common among nilotinib-treated patients (38.6% and 28.8% of patients in the nilotinib and dasatinib cohorts, respectively; $P = 0.008$); the durations of available follow-up data were similar between cohorts (both: median, 22 months). Patients receiving dasatinib more often started at the recommended dose (74.1% vs 53.2%; $P < 0.001$), but they also had more dose reductions ($P = .002$) or increases ($P = .048$) than patients receiving nilotinib. Compared with dasatinib-treated patients, those treated with nilotinib had lower likelihoods of treatment switch (21% [nilotinib] vs 29% [dasatinib]; $P = 0.044$) and discontinuation (59% vs 67%, respectively; $P = 0.026$). Patients treated with either drug had similar levels of treatment adherence. During the 6-month period after the index date, the mean MPRs were 0.79 and 0.81 in the nilotinib and

dasatinib groups, respectively. There was a longer median overall survival and lower risk for mortality in patients treated with nilotinib than in patients treated with dasatinib (median duration of survival: nilotinib, not reached after 4.9 years; dasatinib, 4.0 years [$P = 0.032$]; mortality risk after adjusting for potential confounding factors: 18% vs 28% [$P = 0.008$]). After adjustment for potential confounding factors, patients treated with nilotinib also had fewer inpatient, outpatient, and emergency department visits (all $P < .05$), and the per-patient per-month total medical costs were $513 lower with nilotinib than with dasatinib ($P = 0.024$) (data not shown).[30]

The results from that study highlight several potential contributions of RWE analyses to medical research. No randomized head-to-head trials comparing second-line nilotinib with dasatinib have been conducted; thus, RWE studies such as this one are an important avenue for obtaining comparative analyses. The retrospective collection of information on health care resource utilization and costs provides important insight into the overall economic impact of therapies. Comparable data cannot be readily obtained from RCTs in which patients are treated according to the management policies outlined in the study protocol rather than a physician's professional discretion.

Although retrospective observational health care claims analyses such as the one by our group[30] are valuable, their inherent limitations must also be considered. Variable dosing patterns may have been a factor in the outcomes reported in that study, and the data were limited to those from patients covered by Medicare and information recorded in the Medicare database. Important disease and patient characteristics, such as CML phase, were not included in many claims. Dasatinib is indicated for the treatment of CML in blast crisis, whereas nilotinib is not, and an inability to control for this variable may have skewed the results.

CONCLUSIONS AND FUTURE DIRECTIONS

Conventional RCTs and RWE studies are distinct types of research that produce distinct types of data. Each type is best suited to answering different research questions. When used together, they can provide a fuller picture of the tolerability, efficacy, and overall impact of a drug. Considering the recent publication of guidance documents and commentary from the FDA on topics related to RWE,[1,5,12] it can be expected that RWE will play a growing role in the development of new and existing medical products in the coming years.

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CONFLICTS OF INTEREST

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