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Prospective Benefit-Risk Monitoring of New Drugs for Rapid Assessment of Net Favorability in Electronic Health Care Data

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ABSTRACT

Background: Benefit-risk assessment (BRA) methods can combine measures of benefits and risks into a single value. **Objectives:** To examine BRA metrics for prospective monitoring of new drugs in electronic health care data. **Methods:** Using two electronic health care databases, we emulated prospective monitoring of three drugs (rofecoxib vs. nonselective nonsteroidal anti-inflammatory drugs, prasugrel vs. clopidogrel, and denosumab vs. bisphosphonates) using a sequential propensity score–matched cohort design. We applied four BRA metrics: number needed to treat and number needed to harm; incremental net benefit (INB) with maximum acceptable risk; INB with relative-value–adjusted life-years; and INB with quality-adjusted life-years (QALYs). We determined whether and when the bootstrapped 99% confidence interval (CI) for each metric excluded zero, indicating net favorability of one drug over the other. **Results:** For rofecoxib, all four metrics yielded a negative value, suggesting net favorability of nonselective nonsteroidal anti-inflammatory drugs over rofecoxib, and the 99% CI for all but the number needed to treat and number needed to harm excluded the null during follow-up. For prasugrel, only the 99% CI for INB-QALY excluded the null, but trends in values over time were similar across the four metrics, suggesting overall net favorability of prasugrel versus clopidogrel. The 99% CI for INB-relative-value–adjusted life-years and INB-QALY excluded the null in the denosumab example, suggesting net favorability of denosumab over bisphosphonates. **Conclusions:** Prospective benefit-risk monitoring can be used to determine net favorability of a new drug in electronic health care data. In three examples, existing BRA metrics produced qualitatively similar results but differed with respect to alert generation.

Keywords: benefit risk assessment, prospective monitoring, new drugs.

Introduction

Evidence to support coverage and treatment decisions involving new drugs is predominantly based on data from premarketing randomized controlled trials. Although evidence from randomized trials is critical for regulatory decisions that address whether a drug should be marketed, its utility for postapproval coverage and treatment decisions is more limited because these decisions typically address which treatment to choose. At the time of market authorization, usually little is known about the comparative safety and effectiveness of a new drug versus existing alternatives, especially as they are used in routine practice settings in which patients may differ from those enrolled in the trials [1,2].

Conflicts of interest: J. J. Gagne receives research support from Harvard Catalyst, the US Food and Drug Administration (FDA), the Agency for Healthcare Research & Quality, and the Patient-Centered Outcomes Research Institute. He is a consultant to Aetion, Inc., a software company. D. P. Martin was an employee of Novartis Pharmaceuticals Corporation during the conduct of this study. K. H. Kahler is an employee of Novartis Pharmaceuticals Corporation. S. Schneeweiss is principal investigator of the Harvard-Brigham Drug Safety and Risk Management Research Center funded by the FDA. His work is partially funded by grants/contracts from the Patient-Centered Outcomes Research Institute, the US FDA, and the National Heart, Lung and Blood Institute. He is a consultant to WHISCON, LLC, and to Aetion, Inc., a software manufacturer of which he also owns shares. He is also principal investigator of investigator-initiated grants to the Brigham and Women's Hospital from Novartis and Boehringer Ingelheim, unrelated to the topic of the study.

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To generate additional comparative safety and effectiveness information for new drugs, payers can conduct observational studies in their own routinely collected electronic health care data [3]. Administrative claims data reflect a continuous stream of longitudinal drug and medical service utilization information [4]. Analyses of these data allow payers to assess both benefits and risks of new drugs versus existing alternatives in the same populations of individuals in whom coverage decisions will apply [5,6].

A key benefit of observational analyses in continuously collected electronic data is the ability to identify users of a new medical product and track their outcomes in near real time [7]. This ability to access and analyze data as they accrue has generated considerable interest in methods for sequential analysis of observational data [8–14]. For example, the Food and Drug Administration's Sentinel initiative is developing and implementing a suite of methods to perform prospective surveillance of new medical products in a distributed network of electronic health care databases currently comprising 178 million covered lives [14]. To date, approaches to sequential analysis of new drugs have focused mostly on drug safety surveillance, very little on comparative effectiveness, and even less on simultaneously incorporating benefits and risks into the same active monitoring framework [8,15]. Coverage and treatment decision making, however, requires consideration of both harms and benefits of a new drug versus alternatives.

Sequential analyses with benefit-risk assessment (BRA) methods, which combine measures of benefits and risks into a single numeric index on which to compare the overall benefit-risk profile of one product to another, can aid decision makers in determining whether and when sufficient evidence exists to indicate that one drug is favorable over another. We examined the feasibility of using BRA metrics in this setting by emulating prospective benefit-risk monitoring of three drugs in electronic health care data.

Methods

Using two electronic health care databases, we emulated prospective monitoring of three drugs of interest versus comparators (rofecoxib vs. nonselective nonsteroidal anti-inflammatory drugs [ns-NSAIDs], prasugrel vs. clopidogrel, and denosumab vs. bisphosphonates) beginning at market approval of each drug of interest. For each example, we divided the respective database into smaller data sets defined by calendar periods following approval of the drug of interest and we incorporated each data set into the analysis sequentially to emulate active monitoring of prospectively accruing data.

Databases

Pharmaceutical Assistance Contract for the Elderly program data linked to Medicare data

For the rofecoxib example, we used Medicare Parts A and B data linked to the Pharmaceutical Assistance Contract for the Elderly program drug data for Pennsylvania residents enrolled in both programs. The Pharmaceutical Assistance Contract for the Elderly program provides medications at minimal expense to patients aged 65 years and older with low income but who do not meet the Medicaid annual income threshold. The Medicare Parts A and B data include hospital discharge information and all fee-for-service charges. These data are available as far back as 1994, enabling us to emulate prospective monitoring of rofecoxib when it entered the market in 1999.

MarketScan data

For the prasugrel and denosumab examples, we used 2008 through 2012 data from the Truven Health MarketScan Research databases. These databases contain administrative drug and medical claims data from employers and Medicare for privately insured individuals and for retirees with Medicare supplemental insurance paid by employers, respectively. We used the MarketScan data for these examples because the drugs of interest are more recently marketed.

Examples

Rofecoxib versus ns-NSAIDs

Rofecoxib is a cyclooxygenase-2 inhibitor that causes less gastrotoxicity than do ns-NSAIDs but was withdrawn from the US market because of its association with myocardial infarction (MI). We identified initiators of rofecoxib and ns-NSAIDs (e.g., diclofenac, ibuprofen, meloxicam, nabumetone, and naproxen) between May 1, 1999, when rofecoxib was approved, and September 30, 2004, when rofecoxib was withdrawn from the US market. We defined initiation as a prescription dispensing for rofecoxib or ns-NSAID following a 180-day period with no prescriptions for these drugs. We measured and included in the propensity score (PS) model a large number of potential risk factors for gastrointestinal (GI) bleed and MI, including clinical conditions (e.g., peptic ulcer disease and prior MI) and medications (e.g., anticoagulants and antiplatelets), as well as health service utilization variables (e.g., number of physician visits and number of hospitalizations). All covariates are listed in Appendix Table 1 (in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2015.08.011).

Beginning the day after the initiation date, we followed patients for GI bleed and MI using validated, claims-based definitions that have high positive predictive values (PPVs; 94% for MI [16] and 88% for GI bleed [17]). We censored patients if they died, reached the end of the study period, or at 180 days of follow-up.

Prasugrel versus clopidogrel

Prasugrel and clopidogrel are thienopyridine antiplatelet agents that reduce cardiovascular event risk in patients with acute coronary syndromes (ACS) and that also increase bleeding risk. We identified individuals who initiated prasugrel or clopidogrel following a hospitalization for ACS between July 10, 2009, when prasugrel was approved, and December 31, 2012. We required that patients not have had a prescription for clopidogrel, prasugrel, ticagrelor, cilostazol, or ticlopidine in the 180 days before the first prescription dispensing for one of these drugs following discharge from the ACS hospitalization. We measured a large number of potential risk factors for ischemic and hemorrhagic events (see Appendix Table 2 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2015.08.011).

Beginning the day after the initiation date, we followed patients for the outcomes of MI, ischemic stroke, GI bleed, and hemorrhagic stroke, which we defined using validated definitions with PPVs of 94% [16], 96% [18], 96% [17], and 88% [18], respectively. We censored patients if they died, disenrolled from the database, reached the end of the study period, or at 1 year of follow-up.

Denosumab versus bisphosphonates

Denosumab is a monoclonal antibody used to treat osteoporosis and other diseases of the bone. By acting on the immune system, denosumab might increase the risk of serious infections. We identified initiators of denosumab and bisphosphonates, the most commonly used drugs for osteoporosis, between January 1, 2012, when a J-code for denosumab administration was introduced, and December 31, 2012. We defined initiation as a prescription dispensing for a bisphosphonate or a J-code indicating denosumab injection following a 365-day period with no evidence of use of any osteoporosis drugs. We excluded patients