Conflict of Interest Disclosure in Off-Label Oncology Clinical Trials

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Abstract

Purpose: We sought to determine the prevalence, reliability, and predictors of conflict of interest (COI) and funding disclosure statements for studies of anticancer targeted therapies conducted in the off-label prescribing setting.

Methods: As a part of a federally funded systematic review, manuscripts were included in the analysis if they were used to support one of 19 indications for cancer targeted therapies that were off-label but reimbursable according to compendia published in 2006 or before. Studies were categorized according to trial design, trial results, average impact factor of journals, and presence of COI and funding disclosure statements.

Results: Among the 69 included studies, prevalence of COI and funding disclosures was low, at 33% and 58% respectively; time trends showed some improvement between 2002 to 2007, but only 60% of studies had disclosures by 2007. Predictors of COI disclosure were publication in high-impact-factor journals ($P < .001$), large study sample size ($P = .001$), enrollment exclusively in the United States ($P = .04$), and study of the targeted therapy in combination with other agents as opposed to the study drug alone ($P = .03$).

Conclusion: Disclosure of potential sources of bias in COI and funding statements in studies of off-label indications for anticancer targeted therapies was low and did not increase substantially over time.

Introduction

Off-label prescribing, in which pharmaceutical agents are used for purposes other than those for which the United States Food and Drug Administration (FDA) has granted approval, is common.¹ This practice is especially critical, and has escalated, in oncology where effective treatment options are often limited, prognoses are grim, and there are often several potential uses for new agents. A key driver of the high proportion of off-label prescribing in cancer care is that more than half of all oncology drugs have been approved within the past 15 years, and in that same time period, FDA labels have become increasingly specific.² In 1991, a US General Accounting Office study reported that up to 33% of all cancer drug prescriptions were written for off-label indications.³ By 2005, the proportion rose to 50% to 75%.^{4,5}

For the individual patient, off-label prescribing may be an important therapeutic option. Given the time and resources required to obtain FDA approval, off-label prescribing may be the only viable way for patients to access novel treatments. Typical off-label prescribing scenarios include the treatment of incurable diseases, of rare diseases with few treatment options, and of patients with multiple comorbidities for whom conventional regimens are not appropriate.^{6,7} The majority of patients with cancer receive at least one drug off-label during their course of treatment,^{3,8,9} and for newer targeted oncology drugs (eg, rituximab), off-label prescribing can approach 75%.¹⁰ Off-label prescribing is largely guided by reimbursement policies. Medicare coverage of off-label uses of cancer drugs was stipulated under Social Security Act Section 1861(t)(2)(B)(ii)(I) and (II) under the Omnibus Budget Reconciliation Act of 1993. The statute recognized certain drug compendia as authoritative

sources for determining a “medically-accepted indication” of drugs and biologic agents used off-label for anticancer treatment. In effect, this legislation delegates the responsibility for evidence review, synthesis, and postmarketing recommendations to a handful of compendia.^{11,12} Although the statute pertains specifically to the Centers for Medicare & Medicaid Services (CMS), most other payers and state legislatures follow suit.⁹ The evidence reviewed and included in the approved compendia to support off-label prescribing thus serves as a powerful financial driver of clinical practice and funding of expensive anticancer drugs.

The compendia systematically review the available medical literature to determine the strength of the evidence to support an off-label indication and make recommendations for reimbursement. Systematic evidence review requires assessment of study sponsor to evaluate for potential bias and fully determine whether the strength of evidence supporting an off-label indication is compelling. Similarly, clinicians considering the application of new research to direct patient care need complete conflict and funding information to adequately place evidence in context.

This study is meant to (1) determine the extent to which conflict of interest (COI) and funding are reported in studies of off-label indications for targeted therapies, (2) determine whether the reporting of COI and funding disclosures has changed over time, and (3) explore whether the reporting of COI and funding sources correlates to study design.

Methods

This study extends the technology assessment provided in the “Report on the Evidence Regarding Off-Label Indications for

Targeted Therapies Used in Cancer Treatment,” conducted by the Duke Evidence-based Practice Center under contract to the Agency for Healthcare Research and Quality.¹¹ The report evaluated the state of evidence supporting the use of selected targeted therapies for off-label indications, focusing on eight drugs and 19 specific off-label indications (ie, > one indication per drug).

Included medications were (1) FDA-approved targeted therapies, (2) marketed in January 2007 or before, and (3) compendia-listed for indications other than the FDA-approved indications as of December 2006. Agents were identified through four compendia: American Hospital Formulary Service-Drug Information (AHFS-DI; 2006), National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium (online version), United States Pharmacopeia Drug Information (USP-DI; 2006 version), and Elsevier Gold Standard's Clinical Pharmacology (online version). Collection of abstracts and published reports for review in the literature synthesis was completed on September 14, 2007.

Studies were included if they met all of the following inclusion criteria: (1) conducted in humans; (2) investigated use of one of the eight included targeted therapy drugs for an off-label indication; (3) addressed one of the 19 drug-disease combinations of interest; (4) reported at least one of the following outcomes for efficacy: survival, disease-free survival, tumor response, quality of life, or adverse effects; and (5) were published before September 14, 2007. Exclusion criteria were that the study (1) described only predictors of response, (2) focused on pharmacokinetics (ie, a study in which outcomes are drug levels), or (3) was conducted in a nonhuman setting (ie, animal model or *in vitro*). Analyses were included in this study only if they reported phase II or later study results. These criteria were used to focus on those trials most likely to report funding and COIs.

Data from 69 distinct trials were assembled into a Microsoft Access database. Nine trials had more than one publication of their results, so the duplications were combined into single database entries because they dealt with the same clinical trial. Each study was analyzed for a number of characteristics: whether the trial was blinded, controlled, and/or randomized; location of clinical trial; type of intervention; type of comparator arm; average age of patients; survival assessment; average length of follow-up; average impact factor of journals; and whether there was a funding and COI statement in the published research report. When there was more than one research report for a trial, if any report included a funding or COI statement then the study was scored as having a relevant disclosure.

Analyses focused on funding and COI disclosures in the published research reports. Statistical comparisons were performed using χ^2 tests and Fisher's exact tests, as appropriate, for categorical data, and Student *t* tests for continuous data. All of the categories are mutually exclusive and exhaustive except for site location, in which the category of “both US and non-US” was excluded when performing the statistical test because of the small numbers in this category.

Results

Overall, only 33% of studies had an explicit COI statement, and 58% had an explicit funding disclosure (Table 1). Observation of time trends reveals that the proportion of studies reporting COI and/or funding sources increased between 2002 and 2007, but was only 60% in 2007 (Figure 1).

There were several instances in which the authors' industry involvement was explicitly defined, including 14 instances in which the author was employed by the manufacturer of the drug under investigation, 13 instances in which the company provided research support, 12 instances in which the author served as a consultant, four instances in which the author was involved in data analysis, and three instances in which the author served as a speaker. In four instances, there was no COI statement, but at least one of the authors was employed by the company manufacturing the drug being studied.

Trials with a COI statement tended to be larger, with a median of 51 patients (intra-quartile range [IQR], 25-80) versus 26 patients (IQR, 17-47) for trials without a COI statement, and were published in journals with a higher median impact factor of 17.8 (IQR, 11-18) versus 5.4 (IQR, 2-11), respectively. Both differences were significant, with *P* values of < .001. Similarly, those that reported funding had a higher median patient accrual of 43 patients (IQR, 23-60) versus 21 patients (IQR, 14-47) and were published in journals with a higher median impact factor of 10.6 (IQR, 6.7-17.8) versus 4.6 (IQR, 2.4-5.4).

Studies with a US site were more likely than those with exclusively non-US sites to report a COI (12 of 28 [43%] US sites *v* 6 of 33 [18%] non-US sites; *P* = .04). Studies in which the study drug was tested as part of a combination of chemotherapeutic agents were more likely to report a COI than studies in which the drug was tested alone (16 of 35 [46%] combination treatment *v* 7 of 34 [21%] study drug alone; *P* = .04). Studies with a funding statement were significantly more likely to have more than one clinical trial site (33 of 40 [83%] *v* 16 of 29 [55%]; *P* = .01).

There was no statistically significant difference between study designs in terms of blinding, control, randomization, phase of trial, or comparator in studies with and without a COI or funding statement. Reporting of length of follow-up and overall survival did not vary on the basis of the presence of COI or funding statements.

Discussion

In the published medical literature supporting off-label cancer treatments, the prevalence of COI and funding disclosures was low, at 33% and 58%, respectively. Time trends showed some improvement between 2002 and 2007, but in 2007, only 60% of studies had disclosures, and reporting frequency had leveled off between 2005 and 2007, likely showing the limitations to voluntarily reporting despite the increased emphasis. Larger studies, those published in journals with higher impact factors, and those with more complex regimens were more likely to have statements, as were studies performed in the United States, perhaps as a result of the influence of FDA policies regarding

Table 1. Relationship Between Conflicts of Interest, Funding, and Study Attributes (N = 69 trials)

Trial Characteristic	COI Statement								Funding Statement				
	All Trials		Yes		No		P		Yes		No		P
	No.	%	No.	%	No.	%			No.	%	No.	%	
Blinded							.55						.54
Yes	2	3	0	0	2	100			0	0	2	100	
No	67	97	23	34	44	66			40	60	27	40	
Controlled							.60						.99
Yes	4	6	2	50	2	50			2	50	2	50	
No	65	94	21	32	44	68			38	58	27	42	
Randomized							.60						.99
Yes	4	6	2	50	2	50			2	50	2	50	
No	65	94	21	32	44	68			38	58	27	42	
Comparator arm							.50						.54
Yes	12	17	5	42	7	58			6	50	6	50	
No	57	83	18	32	39	68			34	60	23	40	
Intervention							.03						.89
Study drug	34	49	7	21	27	79			20	59	14	41	
Combination regimen	35	51	16	46	19	54			20	57	15	43	
No. of sites							.71						.01
Single	20	29	6	30	14	70			7	35	13	65	
Multiple	49	71	17	35	32	65			33	67	16	33	
Location of sites							.04						.63
US only	28	41	12	43	16	57			17	61	11	39	
Non-US only	33	48	6	18	27	82			18	55	15	45	
US and non-US	8	12	5	63	3	38			5	63	3	38	
Length of follow-up reported in publication							.39						.53
Yes	35	51	10	29	25	71			19	54	16	46	
No	34	49	13	38	21	62			21	62	13	38	
Median overall survival reported in publication							.61						.24
Yes	30	43	11	37	19	63			15	50	15	50	
No	39	57	12	31	27	69			25	64	14	36	

Abbreviation: COI, conflict of interest.

off-label therapies and the fact that US studies were conducted by more mature organizations and/or investigators.¹³

COI and funding disclosures do not prevent conflicts, but they help to mitigate their impact and allow users of the information,

Figure 1. Trend in funding and COI statement in the off-label literature between 2002 and 2007. COI, conflict of interest.

such as clinicians and publishers of compendia, to make independent judgments about the source and potential impact of sponsorship and financial bias. Recent studies showed that research funded by pharmaceutical companies was more likely to be published, more likely to be associated with restrictions on data sharing and publication, and more likely to have outcomes favoring the sponsor than studies funded by another source.^{14,15} The role of conflicts has also recently been illustrated in the case of a delay in the publication of adverse drug reactions and a case of modification of end points that resulted in obscured results.^{16,17} Users of the medical literature must acknowledge that not all COI is financial; COIs might result from a desire for the prestige of authorship or for academic promotion. Given these dangers, it is important for the reader to at least be aware of potential COIs through author disclosure statements.

Increased reporting of COIs and funding sources fits well with the movement already underway, as an element of the Physician Payments Sunshine Act, to require reporting of “transfers of value” between industry and both physicians and teaching institutions.¹⁸ As outlined in a recent editorial by Carpenter and Joffe in *New*

England Journal of Medicine, unique identifiers that match individual physicians to industry payments could be used to make COI reporting more robust and could be implemented across settings, from grant applications to regulatory findings to manuscripts.¹⁹ If improved reporting in the literature is not done voluntarily, similar legislation may ultimately be passed to require it.

The impact of off-label prescribing of anticancer therapies is beneficial to patients (through access to new treatments for advanced illness), but is also very costly. Targeted therapies are now the fastest growing segment of cancer care, with numerous FDA-approved agents.¹¹ This class accounts for substantial costs to the US health care system. In a study of a monoclonal antibody treatment conducted at a single institution, on-label prescribing increased after the drug's introduction but quickly leveled off, whereas off-label prescriptions exhibited a near-exponential increase.¹⁰ Between 1998 and 2001, direct drug costs for off-label use at that single institution exceeded \$1.1 million, whereas costs for its FDA-approved use totaled \$355,000. Scaled to the national level, and to the full armamentarium of cancer drugs, the cost of off-label prescribing is staggering.

The legislative action that has allowed the compendia to be the authoritative source for reimbursement decisions provides both an efficient mechanism for care and a pathway to promote off-label prescribing outside the purview of the FDA. Given the substantial market for these drugs, the potential for a COI among the compendia is substantial, and public concerns about these conflicts often play out in the news.²⁰⁻²² For example, a 2009 *New York Times* article argued that the system leading to off-label prescribing was fraught with hidden conflicts and called for reconsideration of the compendia-based reimbursement system for off-label prescribing in oncology.²² More transparent disclosure of potential conflicts and funding by the compendia was highlighted as the top priority, with the need for researchers whose studies support off-label prescribing to disclose their conflicts a close second.¹¹ As a clinical research community, we should monitor our own activity, before the lay press, regulatory bodies, and the public demand changes that may not be consistent with quality cancer research and care. The editors of medical journals should also require disclosures, so that a high standard is maintained in the medical literature.

This study is limited by the small number of articles, drugs, and indications in the analysis, and the potential publication bias among the included articles. COI reporting in all venues is becoming more commonplace. However, the study was only conducted through 2007 to avoid summarizing evidence for or against any particular off-label treatment in use today. The goal instead was to outline the trends in reporting standards.

To ensure transparency and to establish confidence in the results of off-label studies, routine COI reporting needs to become standard. Defining appropriate benchmarks for metrics is always hard, but in this case the expectation for COI and funding disclosure should be that it occurs with every publication expected to influence care. We suggest that guidelines require this change. Investigators, authors, and journals need to demand a high level of accountability and consistency in this task. It is important to underscore that the intention of such a guide-

line would not be to expose any suspected wrongdoing, nor would it be to punish those who proceed with research and publication despite conflicts, as such a requirement would significantly limit evidence development. The intention is instead to create a body of literature in the off-label space that is credible and dependable because conflicts are transparent.

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