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Association between conflict of interest and published position on tumor-treating fields for the treatment of glioblastoma*

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ABSTRACT

Objective: To investigate a possible association between authors' financial conflict-of-interest and published position on the clinical application of a medical device utilizing tumor-treating fields (TTF) for the treatment of Glioblastoma.

Methods: We searched Google Scholar for all articles that cite the 2015 JAMA article on TTF in treating glioblastoma. All articles were read in full to identify editorials or review articles that focus on the use of TTF in treating glioblastoma. Selected articles were coded by two investigators as favorable toward the use of TTF, or neutral/ unfavorable. Conflict-of-interest as declared by each author was recorded, and The CMS "Open Payments" Registry was used to independently identify conflict for each listed author of included articles.

Results: There were 15 articles with 44 independent authors included in our analysis. Of the 15 articles, nine articles were categorized as favorable with 35 authors. Of the 35 authors with favorable views, 77% (26/35) had financial conflict-of-interest with the maker of TTF, compared to 11% (1/9) of authors of neutral articles. Authors of articles with a favorable stance towards TTF were more likely to have received payments from the device manufacturer worth greater than 1 000 dollars than authors of neutral articles (66% vs. 0%, p = 0.001). Among the nine favorable articles, 89% (8/9) had at least one author who had received greater than 1 000 dollars from the device manufacturer.

Conclusion: Our study shows an association between authors' published stance on the use of tumor-treating fields for the treatment of glioblastoma and financial ties to the manufacturer of this device.

1. Introduction

Glioblastoma is the most common and most deadly primary central nervous system malignancy. [1] Despite significant resources devoted to this disease and multiple phase III clinical trials conducted over the last 20 years, there have been few treatment advances and overall 5-year survival rates remain poor [2]. Ongoing research has led to the development of therapies and technologies for this illness, including that of tumor-treating fields (TTF). TTF are a novel therapy that is thought to disrupt cell division via the delivery of alternating electric fields through transducer arrays attached to the patient's scalp [3]. This technology is currently available through a single biopharmaceutical company, Novocure.

Following the accumulation of preclinical data demonstrating the in-vitro effect of TTF, this technology was shown to be equivalent to active chemotherapy in recurrent glioblastoma in 2012, [4] and was granted FDA approval for this indication in 2011. Novocure further won FDA approval for the use of TTF in newly diagnosed glioblastoma after a phase III randomized clinical trial, known as EF-14, added TTF to temozolomide and showed a remarkable 4.9-month improvement in median overall survival [5]. More recently, the final analysis of EF-14 was published showing persistence of an overall survival benefit at five years of follow up [6].

Despite these encouraging results, the study received criticism as the trial was industry funded, not sham-controlled, the two groups did not receive the same number of doses of chemotherapy, and the trial

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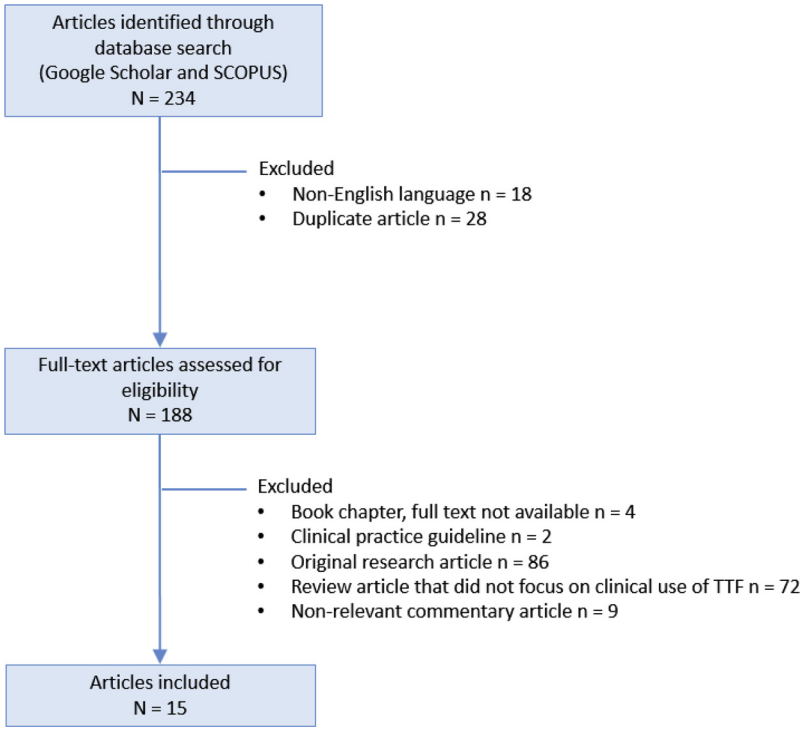

Fig. 1. Flow diagram of study identification, text assessment and exclusion. TTF = Tumor Treating Fields.

was stopped early based on the results of an interim analysis. [7] Further, the cost of this therapy, currently estimated at over 20,000 USD per month, has led many to question whether the benefits are worth the substantial financial burden [8]. Nevertheless, TTF has been included in current NCCN guidelines as a standard treatment regimen for glioblastoma [9].

While the merits of this trial and the appropriate role for TTF in glioblastoma have been debated in the academic community, use of tumor-treating fields has expanded. Novocure reported net revenues of 33 million dollars for the calendar-year 2015, which increased to 82 million dollars for calendar year 2016. [10]

In this study we sought to determine whether financial influence may be shaping the ongoing academic debate surrounding the appropriate place of TTF in current treatment strategies for glioblastoma.

2. Methods

2.1. Search strategy and article selection

On January 11, 2018 we identified all articles on Google Scholar that cite the 2015 JAMA article, *Maintenance Therapy With Tumor-Treating Fields Plus Temozolomide vs Temozolomide alone for Glioblastoma: A Randomized Clinical Trial* [5]. Google Scholar was selected because of its extensive citation network and coverage [11], which specifically for citation analysis is known to be superior compared to other citation engines [11]. A second search was completed using SCOPUS and filtering for all editorials, reviews, and guidelines that referenced the trial. Our search of the SCOPUS database did not reveal any new articles not identified by the initial search.

All articles were individually reviewed for inclusion by title and abstract by one author (M.J.H.). We excluded all articles published in non-English language. Remaining articles were viewed in full. To be included, articles had to be editorials discussing the EF-14 clinical trial, or had to be a guideline or review articles that focused primarily on the use of TTF in clinical practice.

2.2. Data extraction and analysis

Included articles were read independently by two authors (M.J.H. and V.P.). Articles were coded as those that expressed views supportive of TTF without caveat, coded as “favorable”, or those that highlighted any limitations of the device or clinical trial, coded as “neutral”. During review of the 15 included articles, there were no disagreements between each of the authors’ independent reviews.

2.3. Conflicts of interest

After articles had been coded as favorable or neutral, financial conflict of interest as declared by each article was recorded. The Centers for Medicare & Medicaid Services (CMS) “Open Payments” Registry [12] was used to search for payments from Novocure for each US-based author in the included study for all available data from 2013 to 2016 (most recent data available as of time of authorship of this article). All identified payments and the date of the payment were recorded. For authors who could not be identified in the CMS database, we conducted a Google search to identify any unidentified payments. All authors who had no declared conflict of interest or conflict identified through our independent search were coded as having no conflict of interest.

In order to investigate for academic rather than financial conflict, we recorded whether authors were listed as co-authors on the original TTF article relevant to our study.

2.4. Statistical analysis

Statistical analysis was performed using STATA V.13.0. This study was not submitted for institutional board review as it did not involve health care records.

3. Results

Our search strategy yielded 234 individual articles (Fig. 1). Forty-six articles were removed by title and abstract review (18 in non-english language, 28 duplicate articles) leaving 188 articles for full text review.

Seventy-two of these were review articles that did not focus on the clinical use of TTF, two were clinical practice guidelines that did not focus on clinical use of TTF, 86 were original research articles that referenced the subject study, nine were deemed non-relevant editorials, and four were book chapters that were not available via our library services at the time of our study. This yielded 15 individual articles to which 44 individual authors contributed. Nine articles were categorized as favorable, with 35 contributing authors. One author (MM) contributed to two independent articles both categorized as "favorable". The remaining 6 articles were coded as neutral, representing 9 unique authors. Two authors (IZ, JK) contributed to two articles, both described as neutral.

Among the 35 authors of favorable articles, 16 (46%) declared a financial conflict of interest with the device manufacturer in the article. Of the 19 authors who did not declare financial conflict in their relevant article, a search of CMS Open Payments revealed 11 authors who had received funding from Novocure, one who had received no funding, and seven who were not identified on CMS (either non-US based clinicians or non-physicians). Thus, 77% (26 /35) of authors with a favorable stance towards TTF had either declared or independently identified conflict of interest.

Of the 26 authors of favorable articles with declared or identified conflicts with Novocure, 66% (23/35) had identifiable payments in excess of 1 000 dollars and 34% (12/35) received payments greater than 10 000 dollars (Table 1). Of the 11 cases of non-disclosed conflict, nine were valued at over 1000 dollars. In the 9 cases where conflict of interest more than $1000 was not disclosed, we found that the funds from the device maker were received prior to article publication in all nine cases, and was received greater than 1 calendar year prior to publication in eight of these nine cases. Among the nine favorable articles, 89% (8/9) had at least one author who had received greater than 1 000 dollars from the device manufacturer (Table 2).

Among the nine authors of neutral TTF articles, 0% (0/9) declared a financial conflict of interest. A search of CMS showed one author who had received a total of 209 dollars from Novocure for food and beverage, four authors who had received no funding, and four who were not identified on CMS (either non-US based clinicians or non-physicians). No authors of the neutral TTF articles received payments greater than 1000 dollars (Table 1)

A comparison of favorable and neutral articles with the amount of identified conflict present for each article is found in Table 2. Authors of articles with a favorable stance towards TTF were more likely to have received payments from Novocure worth greater than 1 000 dollars than authors of neutral articles (66% vs. 0%, $p = 0.001$).

Among the 44 authors identified in our study, only 2 (RS and AFH) were listed as co-authors on the original TTF article of interest. Both of these authors contributed to articles coded as having a favorable stance toward TTF.

4. Discussion

Our analysis shows a strong association between favorable views of TTF and financial conflicts of interest with the device manufacturer. Articles with neutral views of TTF were, in general, free of financial conflict of interest. In contrast, articles written in favor of TTF uniformly had conflicts greater than $1000 and often undisclosed financial ties to the device manufacturer. Financial conflict of interest largely outweighed the influence of academic conflict of interest in our study. The results of this study suggest that the debate around the use of TTF in academic journals is strongly associated with financial conflicts.

While conflict of interest has been common within the United States healthcare system for the last century, it has come under increasing scrutiny over concerns that industry ties unduly influence public opinion and medical practice. [13] Our data complement other studies showing financial conflicts are associated with an author's stance in biomedical literature [14,15]. Prior work has also linked financial conflict of interest with both clinical trial outcomes [16–18] and physician prescribing practices [19–21]. Overall, we feel the data argue convincingly for stricter and more clear disclosure policies, and for the exclusion of authors with financial conflict of interest from involvement in review articles and clinical practice guidelines that significantly alter clinical practice.

While the results of EF-14 are promising, some researchers may have reasonable reservations about the widespread adoption of TTF for the treatment of glioblastoma based on a single, industry sponsored, unblinded trial that was terminated early. The limitations of EF-14 have not been addressed as Novocure aims to broaden the use of TTF to other solid tumors. There are currently three ongoing phase-3 clinical trials for new indications (pancreatic adenocarcinoma, non-small cell lung cancer, and brain metastases from non-small cell lung cancer), all of which are non-blinded trials. [22] The results of our study underscore the importance of strict disclosure policies and non-biased analyses of these upcoming trials to prevent inappropriate use of a promising new device.

4.1. Limitations

Our study has several limitations. While we used a comprehensive search strategy including two separate search engines, we likely have not included the entirety of positioned views on this topic. Similarly, by excluding original research articles we may not have captured all articles that could have been included, but we felt that this strategy allowed us to focus on articles that focused on the controversy surrounding the use of TTF.

The nature of the articles included also led to an unexpected limitation of our study in that articles in favor of TTF were both more common, and included a larger number of authors that led to a relative imbalance in our comparator groups.

Another limitation is our own potential bias in our subjective assessment of whether an author's position was favorable or neutral. We attempted to limit this bias by coding favorability prior to gathering any financial conflict information, and by coding articles independently.

A final limitation is that we were unable to obtain financial information for every identified author as the CMS database applies only to physicians in the United States. To mitigate over-emphasizing conflict among these authors we coded all authors without identifiable financial ties as having no financial conflict. Our findings may underestimate the degree of financial conflict among the referenced authors.

Table 1
Characteristics of authors of favorable and neutral articles with regard to presence and extent of financial conflict of interest.

	Favorable articles	Neutral articles
Number of authors	35	9
Number of authors who declared financial conflict of interest	16 (46%)	0
Number of authors with undisclosed conflict of interest as identified by our search	11 (31%)	1 (11%)
Number of authors with declared or identified conflict of interest	27 (77%)	1 (11%)
Number of authors who received > 100 dollars in funding from Novocure	24 (69%)	1 (11%)
Number of authors who received > 1 000 dollars in funding from Novocure	23 (66%)	0 (0%)
Number of authors who received > 10 000 dollars in funding from Novocure	12 (34%)	0 (0%)

Table 2
Summary of the degree of conflict of interest identified for each article, categorized by favorable or neutral stance toward use of Tumor Treating Fields.

		Amount of conflict of interest identified on CMS Open Payments in USD
Favorable articles	A state-of-the-art review and guidelines for tumor treating fields treatment planning and patient follow-up in glioblastoma [23]	143 091
	An overview of alternating electric fields therapy (NovoTTF therapy) for the treatment of malignant glioma [24]	141 174
	Tumor treating fields in neuro-oncological practice [25]	85 649
	Alternating electric tumor treating fields for treatment of glioblastoma: rationale, preclinical, and clinical studies [26]	45 574
	Critical review of the addition of tumor treating fields (TTFields) to the existing standard of care for newly diagnosed glioblastoma patients [27]	40 747
	The evolving role of tumor treating fields in managing glioblastoma: guide for oncologists [28]	28 609
	NovoTTF: where to go from here? [29]	11 103
	Perspective on the EF-14 trial and its implications for the role of tumor-treating fields in the management of glioblastoma [30]	4 812
	Tumor treating fields: a novel treatment modality and its use in brain tumors [31]	0
Neutral articles	Tumor treating fields - effective, but at what cost? [32]	209
	Tumor treating fields - a fundamental change in locoregional management for glioblastoma [33]	209
	Living in a material word: tumor-treating fields at the top of the charts [34]	0
	Interpretation of clinical trials that stopped early [35]	0
	Alternating electric fields for the treatment of glioblastoma [36]	0
	TTFields: where does all the skepticism come from? [7]	0

We recognize that the associations between conflict of interest and article position are limited by the observational and descriptive nature of our study. For these reasons we focused our analysis on associations only.

5. Conclusion

Our study shows an association between author's published stance on the use of tumor-treating fields for the treatment of glioblastoma and financial ties to the manufacturer of this new device. We also found substantial unreported conflict of interest. These findings add to a growing body of literature that highlights the need for more clear disclosure policies and unbiased trial analysis for new therapies and technologies.

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