



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Letter to the Editor

Evaluation of financial conflicts of interest and drug statements in the coronavirus disease 2019 clinical practice guideline in Japan

Takanao Hashimoto^{1,2,†}, Anju Murayama^{1,3,*}, Hanano Mamada¹, Hiroaki Saito⁴, Tetsuya Tanimoto⁵, Akihiko Ozaki^{1,6}

¹ Medical Governance Research Institute, Minato City, Tokyo, Japan

² Department of Pharmacy, Sendai City Medical Center, Sendai City, Miyagi, Japan

³ Tohoku University School of Medicine, Sendai City, Miyagi, Japan

⁴ Department of Gastroenterology, Sendai Kosei Hospital, Sendai City, Miyagi, Japan

⁵ Department of Internal Medicine, Navitas Clinic, Tachikawa City, Tokyo, Japan

⁶ Department of Breast Surgery, Jyoban Hospital of Tokiwa Foundation, Fukushima, Iwaki City, Japan

ARTICLE INFO

Article history:

Received 29 July 2021

Received in revised form

14 November 2021

Accepted 14 November 2021

Available online 24 November 2021

Editor: S.J. Cutler

To the editor

Since the coronavirus disease 2019 (COVID-19) outbreak in late 2019, evidence on its treatment has accumulated rapidly. Accordingly, many countries subsequently drafted COVID-specific clinical practice guidelines (CPGs). While CPGs allow healthcare professionals to standardize and improve patient care, inappropriate biases may arise when the authors have financial conflicts of interest (FCOIs) directly related to those recommendations. In Japan, the Ministry of Health, Labour and Welfare (the Ministry) funded the COVID-19 CPG development. Originally published in March 2020, the COVID-19 CPG has undergone multiple revisions. The most recent of these, the fifth edition, was published on 26th May 2021. Consequently, we considered this latest version for this study [1].

We examined all COVID-19 CPG fifth-edition authors and their financial relationships with pharmaceutical companies between 2017 and 2019. These data were voluntarily published by all 79

pharmaceutical companies belonging to the Japanese Pharmaceutical Manufacturers' Association. However, this Association does not impose penalties for non-compliance with the guidelines mandating payment disclosure.

First, we descriptively analysed the authors' demographic characteristics and financial relationships with the pharmaceutical companies manufacturing the drugs listed in the COVID-19 CPG. We also assessed the CPG management policy on FCOIs. We then reviewed the statements of the COVID-19 drugs listed in the CPG and the evidence cited to support them. Details of the methodology are summarized in the [Supplementary Material 1](#).

The 23 COVID-19 CPG authors were all male and content experts. For further details, refer to [Supplementary Material 2](#). Twenty (87.0%) of these authors received at least one payment from a pharmaceutical company. In all, 50 companies (63.3%) made combined payments totalling \$2 823,477, of which \$1 915,196 (67.8%) consisted of scholarship donations, and another \$908 281 (32.2%) were personal payments ([Table 1](#)). The combined 3-year average total payment per author was \$122 760 (standard deviation (SD) \$233 538). Additionally, payments from three of the manufacturers of the COVID-19 drugs included in the CPG ([Supplementary Material Table S3](#)) accounted for 8.4% of the total payments (\$236 294). Of these, Chugai Pharmaceutical Company (the distributor of tocilizumab in Japan) contributed the most at \$153 368, while FUJIFILM Toyama Chemical Company (the manufacturer of favipiravir) paid the least at \$32 574 ([Table 1](#)). Nine authors (39.1%) received at least one payment from these three companies. Since there were no COI statements in the CPG, we contacted the Ministry about its management of CPG author-related FCOIs. Despite four such attempts between June and August, we have received no formal response as of 15th October 2021.

[Supplementary Material 3](#) provides summaries for the drugs recommended in the COVID-19 CPG. As of June 2021, of the five drugs listed in the CPG, remdesivir, dexamethasone, and baricitinib

* Corresponding author. Anju Murayama, Medical Governance Research Institute, 2-12-13 Takanawa, Minato-ku, Tokyo, 1087505, Japan.

E-mail address: ange21tera@gmail.com (A. Murayama).

† Takanao Hashimoto and Anju Murayama contributed equally.

Table 1
Pharmaceutical company author payment breakdown. (n = 23)

| | All companies | Companies manufacturing COVID-19 drugs ^a |
|--|--|---|
| Total payments, US\$ | 2,823,477 | 236,294 |
| Type of payments, US\$ (%) | | |
| Scholarship donations | 1,915,196 (67.8) | 212,751 (90.0) |
| Personal payments | 908,281 (32.2) | 23,543 (10.0) |
| Average (Standard Deviation), US\$ | | |
| Scholarship donations | 83,269 (171,034) | 9250 (24,089) |
| Personal payments | 39,490 (67,676) | 1024 (2599) |
| Overall | 122,760 (233,538) | 10,274 (26,036) |
| Median (Interquartile Range), US\$ | | |
| Scholarship donations | 15,881 (0–87,987) | 0 (0–5411) |
| Personal payments | 13,274 (2289–33,910) | 0 (0–0) |
| Overall | 34,605 (4482–98,020) | 0 (0–6564) |
| Ranking of top five pharmaceutical companies with largest payments (US\$) and recommended drugs if available | | |
| 1st | Nippon Boehringer Ingelheim 343,641 | Chugai Pharmaceutical (Tocilizumab) 153,368 |
| 2nd | Astellas Pharma 163,103 | Eli Lilly Japan (Baricitinib) 50,353 |
| 3rd | Shionogi 155,663 | FUJIFILM Toyama Chemical (Favipiravir) 32,574 |
| 4th | Chugai Pharmaceutical (Tocilizumab) 153,368 | — |
| 5th | Pfizer Japan 152,066 | — |
| Authors with payments (n, %) | | |
| Any payments | 20 (87.0) | 9 (39.1) |
| ≥ \$10,000 | 16 (69.6) | 4 (17.4) |
| ≥ \$50,000 | 9 (39.1) | 2 (8.7) |
| ≥ \$100,000 | 6 (26.1) | 1 (4.3) |

We evaluated the personal payments, including lecturing, consulting, and writing reimbursements, and scholarship donations from pharmaceutical companies using the payment data from 2017 to 2019, which were disclosed on those companies' websites.

Scholarship donations represent funds provided to medical institutions and various departments to encourage educational and academic activities related to the development of new drugs.

Japanese yen (¥) were converted to U.S. dollars (\$) using the 2017 average monthly exchange rate of ¥112.1 per \$1, 2018 average exchange rate of ¥110.4 per \$1, and ¥112.1 per \$1, 2019 average exchange rate of ¥109.0 per \$1. Abbreviation: COVID-19, coronavirus disease 2019.

^a Three pharmaceutical companies were included as companies manufacturing COVID-19 drugs: Eli Lilly Japan K.K. (Baricitinib), Chugai Pharmaceutical Co., Ltd. (Tocilizumab), and FUJIFILM Toyama Chemical Co., Ltd. (Favipiravir). Dexamethasone (DECADRON® Table released in 1959) was previously developed and distributed by MSD K.K. in Japan. However, MSD transferred the manufacturing and marketing approval of dexamethasone to generic companies such as Nichi-Iko Pharmaceutical Co., the largest pharmaceutical companies marketing generic drugs in Japan. Since only generic dexamethasone was available in Japan during the study period we excluded payments from companies marketing dexamethasone from the list of companies manufacturing COVID-19 drugs. Also, Gilead (remdesivir) is not a member of the Japan Pharmaceutical Manufacturers Association, so the payments from this company to healthcare professionals were undisclosed.

received approval for COVID-19 patient treatment in Japan. The other two, tocilizumab and favipiravir, have not. Interestingly, while tocilizumab received a mixture of positive and neutral findings for COVID-19 treatment, the CPG discouraged its use. In contrast, favipiravir received a positive assessment with the embedded description inviting participants in a Ministry-sponsored observational study.

Overall, our study found significant FCOIs between the government COVID-19 CPG authors and pharmaceutical companies. We further note poor management of these FCOIs by the Ministry. The \$39 490 average personal payments and high prevalence of CPG authors with FCOIs were consistent with our previous studies [2,3]. Although government-sponsored CPGs are reportedly more transparent and associated with fewer FCOIs than those not sponsored by the government [4], we did not observe this with the Japanese COVID-19 CPG.

Additionally, we observed inconsistencies between the tone of recommendations and underlying evidence supporting the use of included COVID-19 drugs. For example, the CPG recommended favipiravir without rigorous evidence to support its efficacy. Indeed, neither the World Health Organization nor the United States National Institute of Health have recommended favipiravir. In contrast, tocilizumab was not recommended despite a recent rigorous systematic review confirming its efficacy for the treatment of COVID-19 [5]. Interestingly, while both manufacturers of these drugs made payments to COVID-19 CPG authors, the manufacturer

of tocilizumab paid more. Therefore, the discrepancies in the recommendations suggest that FCOIs do not always result in potentially inappropriate recommendations.

We propose that the Ministry ensures a more transparent and rigorous approach to CPG development. This should include a more balanced author selection process, full COI disclosure, systematic evidence quality assessment, and appropriate recommendations based on established CPG development methodology.

Author contributions

All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. AM, AO and TT: study supervision. TH and AM: statistical analysis. All authors: study concept and design, acquisition, analysis, or interpretation of data, and drafting of the manuscript.

Transparency declaration

As non-financial conflicts of interest, Anju Murayama, Akihiko Ozaki, and Tetsuya Tanimoto have several research articles related to the conflicts of interest among healthcare professionals in Japan. Drs Ozaki and Tanimoto received personal fees from Medical Network Systems outside the scope of the submitted work. Dr Tanimoto also received personal fees from Bionics Co. Ltd, outside the scope of the submitted work. This study was funded in part by the Medical

Governance Research Institute. This non-profit enterprise receives donations from pharmaceutical companies, including Ain Pharmacies, other organizations, and private individuals. This study also received support from Tansa, an independent non-profit news organization dedicated to investigative journalism. However, none of the entities providing financial support for this study contributed to the design, execution, data analyses, or interpretation of study findings and the drafting of this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cmi.2021.11.019>.

References

- [1] Ministry of Health, Labour and Welfare. Coronavirus COVID-19 clinical practice note. 5th edition [In Japanese]. Available at: <https://www.mhlw.go.jp/content/000785119.pdf>.
- [2] Yamamoto K, Murayama A, Ozaki A, Saito H, Sawano T, Tanimoto T. Financial conflicts of interest between pharmaceutical companies and the authors of urology clinical practice guidelines in Japan. *Int Urogynecol J* 2021;32:443–51.
- [3] Kida F, Murayama A, Saito H, Ozaki A, Shimada Y, Tanimoto T. Pharmaceutical company payments to authors of the Japanese clinical practice guidelines for hepatitis C treatment. *Liver Int* 2021;41:464–9.
- [4] Elder K, Turner KA, Cosgrove L, Lexchin J, Shnier A, Moore A, et al. Reporting of financial conflicts of interest by Canadian clinical practice guideline producers: a descriptive study. *CMAJ* 2020;192:E617–25.
- [5] Ghosn L, Chaimani A, Evrenoglou T, Davidson M, Graña C, Schmucker C, et al. Interleukin-6 blocking agents for treating COVID-19: a living systematic review. *Cochrane Database Syst Rev* 2021;3:CD013881.