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Expectations regarding regenerative medicine and attitudes toward invasive surgical therapies in patients with Parkinson's disease: A cross-sectional survey

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ABSTRACT

Introduction: Pharmacological control of the motor symptoms of Parkinson's disease (PD) is challenging with disease progression. Device-aided therapies help relieve these symptoms but are invasive and require specific management. Induced pluripotent stem (iPS) cells avoid ethical concerns and may prevent immune rejection in autologous transplants. Allogeneic iPS cells are considerably more practical, despite potential concerns regarding tumor formation post-transplantation. The present study aimed to clarify the perceptions and acceptance of patients with PD regarding regenerative medicine, invasive surgical treatments (deep brain stimulation, levodopa-carbidopa intestinal gel), and cell transplantation (iPS cells, embryonic stem cells, fetal-derived cells).
Methods: This prospective cross-sectional survey of 102 patients with PD applied a new questionnaire based on a previous survey of the general public's perception of regenerative medicine.
Results: Cell-based therapies were the most popular choice, with 86.1 % of responders choosing it, mainly due to "improvement in quality of life" (69.1 %), "the possibility of slowing the disease progression" (66.2 %), and "treatment effectiveness" (51.5 %). Among these patients, 47.1 % expected regenerative medicine to become the standard therapy within several years and 82.4 % believed that regenerative medicine was safe. Autologous iPS cells were accepted by 83.8 % of the patients, while 52.5 % accepted allogeneic iPS cells.
Conclusions: Patients had high expectations for the therapeutic effects of cell-based therapies and were optimistic about its early implementation and safety in regenerative medicine, with iPS cells being the most accepted for transplantation. The present findings should be confirmed in a larger cohort, as these findings are based on a limited sample.

1. Introduction

The first treatment choice in patients with Parkinson's disease (PD) is pharmacological therapy to supplement deficient dopamine levels; however, with disease progression, controlling motor symptoms with oral medication alone becomes challenging [1–4]. In advanced PD, invasive therapies like deep brain stimulation (DBS) and levodopa-carbidopa intestinal gel (LCIG) are used in addition to oral medication [5,6]. DBS reduces off symptoms and dyskinesias by implanting electrodes in the brain and a stimulator in the chest, which requires patients to undergo brain surgery and device replacement [7,8]. LCIG delivers medication directly to the jejunum via a surgically placed tube and pump, extending symptom relief but requiring skill to operate as well as daily cassette changes [9–11]. Thus, while these device-aided therapies help relieve symptoms, they are invasive and require specific management.

Cell-based therapies for PD, which involves the transplantation of dopamine-producing nerve cells directly into the brain, have been

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researched since the 1980s, with ongoing clinical trials to assess its efficacy and safety [12–14]. Early experiments in the late 1980 s used fetal-derived cells in Northern Europe, raising ethical concerns regarding the source of these cells [15–18]. Embryonic stem (ES) cells, derived from blastocysts, can be maintained indefinitely under proper culture conditions and are currently used in clinical trials for PD [19]. Induced pluripotent stem (iPS) cells, generated from somatic cells, avoid ethical concerns and may theoretically prevent immune rejection in autologous transplants derived from the patient's own cells [20]. However, allogeneic iPS cells derived from other people's cells are considered more practical due to safety and cost, which generally require immunosuppressants [21]. Even if innovative methodologies significantly reduce the cost of generating autologous iPS cells, considering the genetic risks involved in familial PD and safety assessments, allogeneic iPS cells offer more advantages than autologous iPS cells. Additionally, the reprogramming of iPS cells is not fully understood, and potential concerns are pointed out about tumor formation after transplantation. Despite these concerns, public interest in regenerative medicine remains high [22,23], highlighting the need for cautious information.

In the present study, our primary aim was to clarify the perceptions of patients with PD regarding regenerative medicine and invasive surgical treatments (such as DBS and LCIG), and their acceptance of cells used for transplantation (iPS cells, ES cells, and fetal-derived cells). As overly high expectations may impede sharing of attainable treatment goals with patients, understanding patients' expectations allows us to provide better information and share appropriate treatment goals.

2. Methods

2.1. Recruitment and data collection

This prospective cross-sectional survey recruited patients with PD aged ≥20 years at Kyoto University Hospital (KUHP: Kyoto, Japan) who met the following criteria: PD diagnosis according to the Movement Disorder Society (MDS) Clinical Diagnostic Criteria [24] and no significant cognitive decline as judged by their attending physician. Eligibility details are presented (Supplementary Methods).

We collected questionnaires on paper or online using Google Forms at KUHP from April to December 2020 and at other locations from May 2020 to March 2023 (Supplementary Methods). This study was approved by the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine, approval number R2335-7.

2.2. Questionnaire

We developed a new questionnaire based on a previous survey that assessed the general public's perceptions of regenerative medicine [23]. Neurologists verified whether the questionnaire to ensure was suitable for patient self-administration. The questionnaire consisted of four sections: preferences regarding invasive surgical therapies, attitudes toward regenerative medicine, acceptance of the cells used in cell-based therapies, and patient background.

The preferences regarding invasive surgical therapies section asked respondents whether they would consider the treatment options for cell-based therapies, DBS, and LCIG by selecting "strongly agree," "agree," "reluctantly agree," or "absolutely disagree." The option "already undergone the treatment" was available only for DBS and LCIG, as none of the participants had undergone cell-based therapies. Since it is currently difficult to determine whether patients who have already undergone device-aided therapies can undergo other invasive treatments, patients who had already received DBS or LCIG were excluded when examining treatment preferences. Participants who chose "absolutely disagree" were asked to select from multiple options to explain their reasons for disagreement. Anticipating that many patients would be interested in opting for cell-based therapies, those who selected "strongly agree," "agree," or "reluctantly agree" were also asked to provide their reasons by choosing from multiple options.

The attitude toward regenerative medicine section consisted of six questions (Table S1). Respondents chose from multiple options based on those used in the previous survey questionnaires [23].

The acceptance of cells used in the cell-based therapies section asked the respondents whether they would choose the following four types of cells—autologous iPS cells, allogeneic iPS cells, ES cells, and fetal-derived cells—for transplantation and their reasons for these selections. For each cell type, the respondents selected four options: "acceptable," "slightly acceptable," "slightly unacceptable," and "unacceptable." Respondents who chose "slightly unacceptable" or "unacceptable" were asked to select their reasons from multiple options.

The patient background section included items inquiring about PD status, including the self-reported Hoehn and Yahr stage, the presence of off symptoms or dyskinesia, and the level of caregiving required. Given the potential variability in patient knowledge of regenerative medicine, cell-based therapies, and transplanted cells (iPS cells, ES cells, and fetal-derived cells), all participants were provided with standardized information on the topic prior to completing the questionnaire based on information from the regenerative medicine portal (Supplementary Information 1∼3). It also provided details on DBS and LCIG, including the risks, benefits, and necessary procedures. In outpatient settings, staff assisted with reading and writing when needed. Data analysis was conducted using descriptive statistics, specifically frequencies and percentages.

3. Results

The demographic data of the 102 respondents who participated in the survey are summarized in Table 1 (2 patients unanswered demographic data). The response rates varied by question because of the exclusion of non-respondents. Of all respondents, 79 (77.5 %) completed the questionnaire independently, while 23 (22.5 %) completed it with family assistance. Additionally, 89 (87.3 %) attended KUHP outpatient services, and 13 (12.7 %) had participated in patient associations or informational meetings. Out of 102 respondents, 79 had not undergone device-aided therapy, 19 had received DBS treatment, 1 had undergone LCIG treatment, and 3 patients had partially missing responses.

3.1. Preferences regarding invasive surgical therapies

Cell-based therapies were the most popular choice, with 68 out of 79 responders (86.1 %) choosing it (by selecting "strongly agree," "agree," or "reluctantly agree" in their responses to treatment choice), while 44

Table 1
Demographics and clinical characteristics of patients with Parkinson's Disease (n = 102).

Variable		N	%
Sex***	Male	37	37.0
	Female	63	63.0
Age (years)***	≦50 s	16	16.0
	60 s	36	36.0
	70 s≦	48	48.0
Age at diagnosis (years)***	≦50 s	55	55.0
	60 s	33	33.0
	70 s≦	12	12.0
Education (years)***	≦12	36	36.0
	>12	64	64.0
Self-reported HY[a]**	<3	49	49.5
	3≦	50	50.5
OFF symptoms*	−	36	36.7
Dyskinesia*	−	66	67.3
Caregiving required**	+	62	62.6

[a] HY: Hoehn and Yahr stage. Due to missing data, items indicated by * correspond to n = 98, ** to n = 99, and *** to n = 100.

out of 79 (55.7 %) responders selected DBS and 35 responders (44.3 %) selected LCIG (Fig. 1). In this study, 21 (26.6 %), 5 (6.3 %), and 1 (1.3 %) out of 79 responders selected "strongly agree" for cell-based therapies, DBS, and LCIG, respectively. Nine out of 79 respondents (11.4 %) were from outside KUHP. Among them, 6 (66.7 %) chose cell-based therapies by selecting "strongly agree," "agree," or "reluctantly agree" in their responses to treatment choice. Meanwhile, 4 out of 9 (44.4 %) respondents selected DBS, and 5 (55.6 %) selected LCIG. Out of 9 respondents, 2 (22.2 %) selected "strongly agree" for cell-based therapies, while none selected "strongly agree" when considering DBS or LCIG.

The preferred order of treatment options remained the same when we divided the patients into subgroups based on sex, age, years of education, self-reported Hoehn and Yahr stage, presence of off symptoms or dyskinesia, and level of caregiving required (Fig. 2), except for patients with PD diagnosed in their 70 s, who equally favored DBS and LCIG.

The reasons why patients with PD did not want to choose device-aided therapies included concerns about device invasiveness and convenience (Table S2). The reasons for not choosing DBS (by selecting "absolutely disagree": n = 35) were its invasiveness, including "implantation of a device" (n = 22, 62.9 %), "neurosurgery" (n = 21, 60.0 %), and "stimulator replacement" (n = 16, 45.7 %). Another reason for not choosing DBS was "preference for oral medication therapy only" (n = 17, 48.6 %). The reasons for not choosing LCIG (by selecting "absolutely disagree": n = 44) included the inconvenience of LCIG for "carrying a device" (n = 28, 63.6 %) and "daily cassette replacement" (n = 27, 61.4 %), and "abdominal surgery" (n = 23, 52.3 %). The most common reason for not choosing cell-based therapies (by selecting "absolutely disagree": n = 11) was "insufficient accumulation of knowledge" (n = 11, 100 %). Other reasons for not choosing cell-based therapies included "neurosurgery" (n = 9, 81.8 %) and "preference for oral medication therapy only" (n = 9, 81.8 %), as in DBS.

In contrast, the reasons for choosing cell-based therapies (by selecting "strongly agree," "agree," or "reluctantly agree": n = 68 in total) were "improvement in quality of life" (n = 47, 69.1 %), "the possibility of slowing the disease progression" (n = 45, 66.2 %), and "treatment effectiveness" (n = 35, 51.5 %) (Table S3). Other reasons for choosing cell-based therapies included "ameliorating off symptoms" (n = 28, 41.2 %) and "avoiding an increase in medications" (n = 26, 38.2 %).

3.2. Attitudes towards regenerative medicine

Most patients were knowledgeable about regenerative medicine. Only a few patients reported not knowing about regenerative medicine, iPS cells, or cell-based therapy using iPS cells (5.9 %, 2.0 %, and 5.9 %, respectively). In this study, 48 out of 102 responders (47.1 %) expected regenerative medicine to become the standard therapy within several years (Fig. S1A). Regarding technological changes in regenerative medicine over the next 10 years, 61 out of 101 responders (60.4 %) thought that regenerative medicine would improve their quality of life (Fig. S1B). However, 25 out of 101 responders (24.8 %) chose options that reflected excessive expectations: 16 out of 101 responders (15.8 %) answered that hospitals would no longer be necessary, and 9 (8.9 %) answered that damaged organs could be replaced. Concerning safety, 84 out of 102 responders (82.4 %) answered that regenerative medicine is safe ("strongly agree": n = 27, 26.5 %; "somewhat agree": n = 57, 55.9 %). Furthermore, 55 out of 102 responders (53.9 %) displayed a positive attitude toward regenerative medicine ("it is important to consider safety but promoting regenerative medicine is beneficial"), 37 responders (36.3 %) had safety concerns ("there are some safety concerns, the use of regenerative medicine is inevitable"). Finally, many patients were keen to learn about "risks," "cost of treatment," and "means of ensuring safety," whereas fewer were interested in the "benefits," "ethical issues," or "history of researches" of regenerative medicine (Table S4).

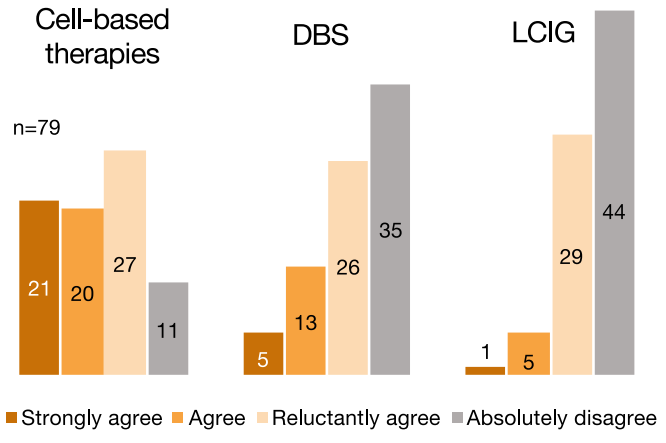

Fig. 1. Preferences Regarding Invasive Surgical Therapies. Respondents were asked whether they would consider treatment options including cell-based therapies, deep brain stimulation (DBS), and levodopa-carbidopa intestinal gel (LCIG). The numbers represented the number of respondents.

3.3. Acceptance of cells used in transplantation

In this study, 83 out of 99 responders (83.8 %) accepted autologous iPS cells, while 52 responders (52.5 %) accepted allogeneic iPS cells (by selecting "acceptable" or "slightly acceptable"). The total of 99 reflects the exclusion of missing data. ES cells were accepted by 36 responders (36.4 %), and fetal-derived cells accounted for 30 responders (30.3 %) (Fig. 3). The main reason for rejecting autologous iPS cells ("slightly unacceptable" or "unacceptable": n = 16) was "insufficient clinical application knowledge" (n = 8, 50.0 %). The reasons for rejecting allogeneic iPS cells ("slightly unacceptable" or "unacceptable": n = 47) included "use of immunosuppressant medication" (n = 29, 61.7 %), "resistance to using cells from another person" (n = 25, 53.2 %), and "choice of autologous iPS cells" (n = 22, 46.8 %). ES and fetal-derived cells also had similar reasons for patient rejection ("slightly unacceptable" or "unacceptable" ES: n = 63, fetal-derived: n = 69), including "use of immunosuppressant medication" (ES: n = 33, 52.4 %; fetal-derived: n = 36, 52.2 %), "psychological resistance to the cell source" (ES: n = 27, 42.9 %; fetal-derived: n = 34, 49.3 %), and "choice of autologous iPS cells" (ES: n = 40, 63.5 %; fetal-derived: n = 41, 59.4 %).

4. Discussion

The results of this study demonstrated that cell-based therapies are highly favored among patients with PD, ranking above device-aided therapies such as DBS and LCIG. This preference was consistent across different patient demographics, including sex, age, years of education, Hoehn and Yahr stage, presence of off symptoms or dyskinesia, and the level of caregiving required. Patients chose cell-based therapies because of its therapeutic effects, quality of life improvements, and the potential to slow disease progression. Regarding technological changes in regenerative medicine, 24.8 % of responders chose options that reflected excessive expectations ("no hospitalization required": 15.8 %, "replacement of damaged organs": 8.9 %). Additionally, 47.1 % of responders anticipated its clinical application within several years. These findings highlight the need for effective communication during informed consent and patient education, taking into account the possibility that patients may hold overly optimistic expectations that exceed the realistic potential of current therapies. Patients favored autologous iPS cells for cell transplantation, followed by allogeneic iPSCs, ES cells, and fetal-derived cells. The reasons for avoiding DBS and LCIG included the invasiveness of the procedure and inconveniences.

Patients with PD preferred cell-based therapies to conventional device-aided therapies because they expected high therapeutic effects.

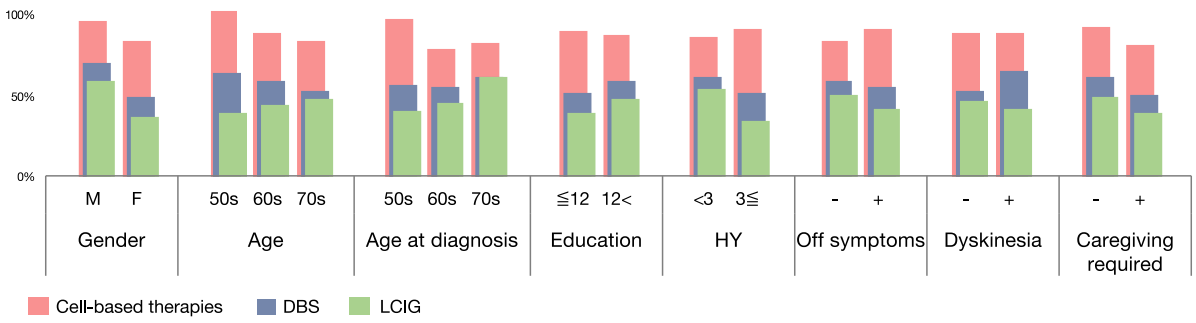

Fig. 2. Treatment Preferences Categorized by Patient Background. Respondents who selected "strongly agree," "agree," or "reluctantly agree" for each treatment option (i.e. cell-based therapies, Deep Brain Stimulation (DBS) and Levodopa-Carbidopa Intestinal Gel (LCIG)) were categorized by patient background. The bars are represented as percentages, with a sample size of 78.

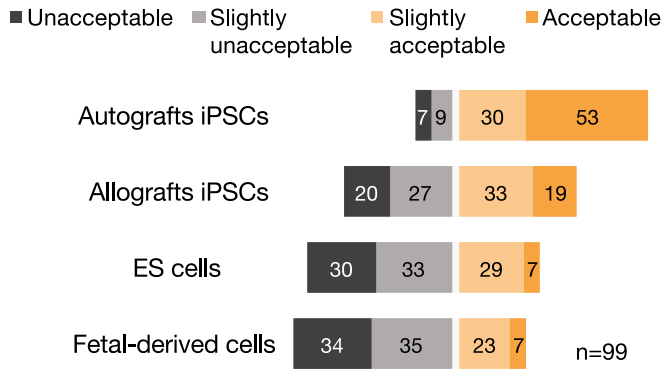

Fig. 3. Acceptance of Cells Used in Transplantation. The respondents were asked whether they would accept cell-based therapies, using autograft induced pluripotent stem (iPS) cells, allograft iPS cells, and embryonic stem (ES) cells. The numbers represented the number of respondents.

DBS is a standard treatment, yet only 55.7 % of responders in the present study chose it ("strongly agree," "agree," or "reluctantly agree"). In contrast, 86.1 % opted for cell-based therapies ("strongly agree," "agree," or "reluctantly agree"), which also requires invasive brain surgery. The reasons for choosing cell-based therapies included higher expectations for treatment efficacy rather than interest in new treatments (improvement in quality of life: 69.1 %, the possibility of slowing disease progression: 66.2 %, treatment effectiveness: 51.5 %, and trying new treatment: 26.5 %). Surveys in South Korea revealed significant patient optimism for unapproved stem cell therapy. One report found that 55.3 % of patients with PD were willing to undergo experimental stem cell treatment [25]. These findings were consistent with a survey showing that 46 % of patients with stroke were interested in trying unapproved stem cell treatments, even without sufficient knowledge of the potential side effects, while only 26 % of physicians recommended these treatments [26].

Patients with PD may exhibit optimism regarding the early adoption and safety of regenerative medicine, potentially leading to an underestimation of the associated drawbacks and concerns. As per our survey, 82.4 % of patients with PD agreed with the safety of regenerative medicine (strongly agree, 26.5 %; somewhat agree, 55.9 %). In contrast, a previous survey targeting general public populations in various countries found that only 51 % of Japanese respondents considered regenerative medicine to be safe, with only 9 % fully agreeing and 42 % somewhat agreeing [27]. Our survey findings revealed that 47.1 % of patients with PD anticipated the realization of regenerative medicine within several years. Conversely, a survey targeting the general population showed that only 32.1 % of citizens and 20.3 % of scientists affiliated with the Japanese Society of Regenerative Medicine believed in such early implementation [23]. In our survey, 53.9 % of patients with PD supported the promotion of regenerative medicine while considering safety, compared with only 27.0 % of the general public in previous survey [27]. Additionally, 36.3 % of the patients in the present study had safety concerns but saw its use as inevitable, whereas 48.0 % of the general public held this view.

While expectations for regenerative medicine were high, patients were aware of the associated risks. The information most desired by patients included "risks," "cost of treatment," and "means of ensuring safety," indicating that patients recognize the importance of this information when considering treatment options. A previous public survey on regenerative medicine also highlighted similar concerns, such as its risks and costs [23].

Among cell-based therapies for PD, iPS cells were more accepted than other cell types; however, the fact that allogeneic iPS cells are more likely to be used soon owing to safety and cost reasons requires further explanation. Our results revealed that iPS cells were accepted in 83.8 % of autologous transplants and 52.5 % of allogeneic transplants, making them more acceptable than ES (36.4 %) and fetal-derived cells (30.3 %). In a survey of Swedish citizens, 70 % accepted the use of ES cells for therapeutic purposes, a rate that dropped to 40 % when iPS cells were available [28]. Although iPSCs were more accepted than ES cells, autologous iPSCs had a higher acceptance rate than allogeneic ones. Previous research on skin tissue engineering revealed that skin tissue created from a patient's cells was accepted by 92.8 % of outpatient clinic patients, compared with 47.0 % for tissue derived from donor cells [29]. In the same study, the acceptance rate for using cells from other people (69.2 %) was lower than that for using cells from oneself (93.9 %) for PD treatment, thus demonstrating a difference in acceptance.

In this study, patients with PD preferred DBS to LCIG. One reason for this preference may be the lack of need for device management. LCIG requires external device management and daily cassette changes, whereas DBS involves concerns about the invasiveness of neurosurgery and device implantation but does not require daily device management. Concerns about LCIG were more focused on the convenience of carrying and changing the cassette than on gastrostomy surgery.

This study has some limitations. First, the respondents in this study were predominantly from KUHP who conducts clinical trials on allogeneic iPSC-based therapy. Therefore, the sample were potentially more interested in cell-based therapies and regenerative medicine, possibly leading to higher expectations. Despite the limited sample size, patients outside KUHP also tended to prefer cell-based therapies. For patients with various disease backgrounds, factors such as being male, older respondents, having a higher level of education, a longer duration of illness, and more severe symptoms are associated with greater acceptance of stem cell research among patients [30]. In this survey as well, the acceptance of cell-based therapies was higher among male patients, those with more severe HY stages, and those experiencing off symptoms. Additionally, in this survey, cell-based therapies emerged as the most preferred choice among patients with PD, regardless of patient background. Notably, this trend was observed in where cell-based therapies

remained the most favored choice even among female patients, younger patients, those with lower education levels, a lower self-reported Hoehn and Yahr stage, absence of dyskinesia, and a lower level of caregiving required (Fig. 2). Second, only 20 participants had received DBS or LCIG, and this study may underrepresent the perspectives of patients who have experienced these interventions. Third, this study included a high proportion of female participants. Influence of this skew was likely to be minor since both sexes showed a consistent preference for cell transplantation. In any case, future studies involving broader and more diverse populations should be necessary.

In conclusion, patients had high expectations of the therapeutic effects of cell-based therapies and were optimistic about its early implementation and safety in regenerative medicine. However, they were soberly aware of the risks associated with regenerative medicine. Among cells used for transplantation, iPS cells were the most accepted by patients with PD and autologous iPS cells were more accepted than allogeneic cells. With these in mind, clinicians can help align patient expectations with realistic treatment possibilities through careful and thoughtful clinical communication.

5 Ethical compliance statement

This study was approved by the Institutional Review Board (IRB) of Kyoto University Graduate School and Faculty of Medicine. (Approval No.: R2335-7). Written informed consent was obtained from patients participating in the in-person questionnaire collection due to the potential for identification of individuals. For other patients, consent was inferred from their participation, as data collection was conducted anonymously. We have read the journal's position on issues involved in ethical publication and confirm that this report is consistent with those guidelines.

Funding sources and conflict of interest

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CRediT authorship contribution statement

Mika Watabe: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Atsushi Shima:** Writing – review & editing, Resources, Formal analysis, Conceptualization. **Kiyoaki Takeda:** Methodology, Conceptualization. **Yuta Terada:** Methodology, Conceptualization. **Yusuke Sakato:** Methodology, Conceptualization. **Akira Nishida:** Methodology, Conceptualization. **Ikko Wada:** Methodology, Conceptualization. **Haruhi Sakamaki-Tsukita:** Methodology, Conceptualization. **Kenji Yoshimura:** Methodology, Conceptualization. **Kambe Daisuke:** Methodology, Conceptualization. **Koji Furukawa:** Methodology, Conceptualization. **Masanori Sawamura:** Writing – review & editing, Resources, Formal analysis, Conceptualization. **Etsuro Nakanishi:** Writing – review & editing, Resources, Formal analysis, Conceptualization. **Yosuke Taruno:** Writing – review & editing, Resources, Formal analysis, Conceptualization. **Hodaka Yamakado:** Writing – review & editing, Resources, Formal analysis, Conceptualization. **Ryosuke Takahashi:** Writing – review & editing, Resources, Formal analysis, Conceptualization. **Nobukatsu Sawamoto:** Writing – review & editing, Resources, Formal analysis, Conceptualization.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author used Chat GPT in order to assistance in drafting English text. After using this tool/service, the author reviewed and edited the content as needed and take full responsibility for the content of the publication.

Data availability

The data supporting the findings of this study are available from the corresponding author upon request.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Nobukatsu Sawamoto reports financial support was provided by JSPS KAKENHI. Nobukatsu Sawamoto reports financial support was provided by Japan Agency for Medical Research and Development. Hodaka Yamakado and Ryosuke Takahashi reports financial support was provided by Japan Science and Technology Agency. Ryosuke Takahashi reports financial support was provided by MHLW Research on rare and intractable diseases Program. Ryosuke Takahashi and Nobukatsu Sawamoto reports a relationship with Sumitomo Pharma Co Ltd that includes: funding grants. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.prdoa.2025.100341.

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