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Dynamic chest radiographic evaluation of the effects of tiotropium/olodaterol combination therapy in chronic obstructive pulmonary disease: the EMBODY study protocol for an open-label, prospective, single-centre, non-controlled, comparative study

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ABSTRACT

Introduction To date, there is limited evidence on the effects of bronchodilators on respiratory dynamics in chronic obstructive pulmonary disease (COPD). Dynamic chest radiography (DCR) is a novel radiographic modality that provides real-time, objective and quantifiable kinetic data, including changes in the lung area (Rs), tracheal diameter, diaphragmatic kinetics and pulmonary ventilation during respiration, at a lower radiation dose than that used by fluoroscopic or CT imaging. However, the therapeutic effect of dual bronchodilators on respiratory kinetics, such as chest wall dynamics and respiratory muscle function, has not yet been prospectively evaluated using DCR.

Aim This study aims to evaluate the effects of bronchodilator therapy on respiratory kinetics in patients with COPD using DCR.

Methods and analysis This is an open-label, prospective, single-centre, non-controlled, comparative study. A total of 35 patients with COPD, aged 40–85 years, with a forced expiratory volume in the first second of 30–80%, will be enrolled. After a 2–4 weeks washout period, patients will receive tiotropium/olodaterol therapy for 6 weeks. Treatment effects will be evaluated based on DCR findings, pulmonary function test results and patient-related outcomes obtained before and after treatment. The primary endpoint is the change in Rs after therapy. The secondary endpoints include differences in other DCR parameters (diaphragmatic kinetics, tracheal diameter change and maximum pixel value change rate), pulmonary function test results and patient-related outcomes between pre-therapy and post-therapy values. All adverse events will be reported.

Ethics and dissemination Ethical approval for this study was obtained from the Ethics Committee of Chiba University Hospital. The results of this trial will be published in a peer-reviewed journal.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Dual-inhaled bronchodilators are commonly used to treat chronic obstructive pulmonary disease, as they improve lung function and reduce symptoms and exacerbations. However, the therapeutic effect of dual bronchodilators on respiratory kinetics, such as chest wall dynamics and respiratory muscle function, is yet to be prospectively evaluated by dynamic chest radiography.

WHAT THIS STUDY ADDS

⇒ To our knowledge, this is the first prospective study that will elucidate the effects of dual bronchodilators on respiratory kinetics using dynamic chest radiography.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ As the response to bronchodilators varies among patients with chronic obstructive pulmonary disease, this study could provide additional evidence for the potential to use dynamic chest radiography to optimise bronchodilator therapy.

Trial registration number jRCTs032210543.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the leading cause of morbidity and mortality worldwide. COPD is characterised by persistent symptoms and airflow limitation. Inhaled bronchodilator medications are central to the management of COPD and are

frequently prescribed to prevent or reduce symptoms and exacerbations.[1] In comparison with mono bronchodilators, dual bronchodilators with a long-acting β2-agonist (LABA) and long-acting muscarinic antagonist (LAMA) may be more effective in alleviating symptoms and exacerbations. A previous study reported improvements in forced expiratory volume in 1 s (FEV_1), functional residual capacity (FRC) and residual volume (RV) at the peak and trough following treatment with dual bronchodilators, tiotropium (LAMA)/olodaterol (LABA) (T/O), compared with tiotropium or olodaterol alone, with no observed differences in tolerability.[2]

The limitation of the modalities for assessing the effects of bronchodilators is a substantial concern when there is need for COPD treatment guidance. While pulmonary function tests (PFTs) are commonly used, changes in PFT results only weakly correlate with changes in clinical outcomes, such as patient symptoms and quality of life, following bronchodilator use.[3 4] Despite the recommendations in the guidelines, PFTs are underused in the diagnosis and monitoring of patients with COPD.[5] Thus, there is a need for additional examinations, such as lung imaging or biomarker measurements, for an easy, safe and more comprehensive assessment of treatment efficacy in patients with COPD.

Dynamic chest radiography (DCR) is a novel functional radiographic imaging technique that provides objective and quantifiable real-time chest cavity data, including pulmonary ventilation and circulation, cardiovascular function and diaphragmatic kinetics, at a radiation dose 10 times lower than that used for fluoroscopic or CT imaging.[6–8] Several studies have implemented this technique for functional analysis in COPD. DCR has revealed that diaphragmatic motion during tidal or forced breathing is significantly altered in COPD.[9 10] The rate of change in lung area (Rs ratio) due to respiratory motion from maximum inspiration to maximum expiration evaluated with DCR reflects air trapping and is associated with %FEV_1 in patients with conditions causing airflow limitation, including COPD.[11] DCR has also shown that changes in the tracheal diameter during deep breathing are significantly greater in patients with airflow limitation than in those with normal pulmonary function.[12] DCR can detect changes in X-ray translucency (radiographic pixel value) associated with air ventilation, perfusion and mismatch of ventilation and perfusion.[6 13–15] Air ventilation, assessed by craniocaudal gradients of the maximum pixel value change rate (MPCR) during breathing, was found to be significantly decreased in COPD.[16] In addition, DCR has revealed improvements in diaphragmatic kinetics and range of chest wall movement during respiration after treatment for cystic fibrosis.[17 18] Recently, DCR was demonstrated to be effective in the verification of COPD therapy efficacy in two clinical cases.[19]

These results suggest that DCR may be a useful tool for detecting chest kinetic abnormalities and assessing therapeutic effects on lung mechanics in lung diseases, including COPD. Nevertheless, the therapeutic efficacy of dual bronchodilators on respiratory kinetics assessed by DCR and the correlation of DCR findings with PFT results and patient-related outcomes (PROs) have not yet been prospectively examined in patients with COPD.

To our knowledge, this will be the first study to evaluate the therapeutic effects of dual bronchodilators on respiratory kinetics in patients with COPD using DCR.

Furthermore, we will examine the efficacy of T/O in reducing the FRC and RV, as its effectiveness remains to be elucidated in Japan.

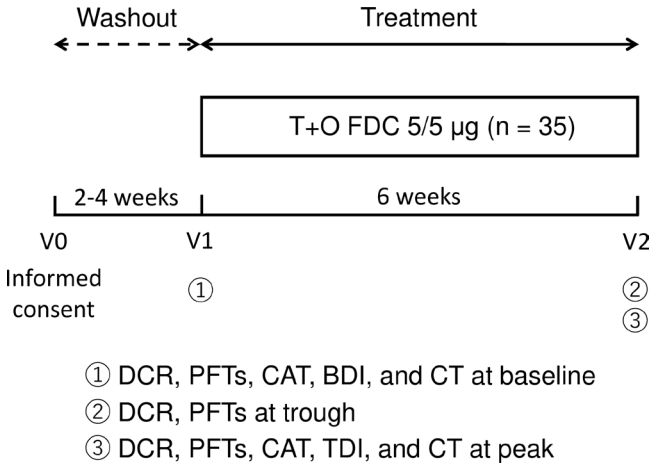

Figure 1 The EMBODY study design. This is an open-label, prospective, single-centre, non-controlled, comparative study with examinations conducted before and after treatment. The treatment consisted of the administration of a 5/5 μg inhalation solution of tiotropium/olodaterol (T/O) (2.5/2.5 μg per actuation) using a soft-mist inhaler once a day. After a 2–4 weeks washout period, patients with COPD will receive T/O for 6 weeks. The effect of treatment will be evaluated using DCR, PFTs, CAT, BDI, TDI and CT before and 6 weeks after receiving the treatment. The DCR, PFT, CAT, BDI and CT findings will be examined at baseline. At Visit 2, DCR and PFTs will be performed at the trough (24 hours after the last administration of T/O), and DCR, PFTs, CAT, TDI assessment and CT will be performed at the peak (2 hours 30 min after inhalation of T/O). BDI, Baseline Dyspnoea Index; CAT, COPD assessment test; COPD, chronic obstructive pulmonary disease; DCR, dynamic chest radiography; FDC, fixed-dose combination; O, olodaterol; PFTs, pulmonary function tests; T, tiotropium; TDI, Transition Dyspnoea Index; V, visit.

METHODS AND ANALYSIS

Study design

This will be an open-label, prospective, single-centre, non-controlled, comparative study, with examinations conducted before and after treatment. The treatment will consist of the administration of a 5/5 μg inhalation solution of T/O (2.5/2.5 μg per actuation, two actuations per treatment) using a soft-mist inhaler once a day. After a 2–4 weeks washout period, patients with COPD will receive T/O for 6 weeks (figure 1). DCR, PFTs, COPD

assessment test (CAT), Baseline Dyspnoea Index (BDI) assessment and CT will be performed at baseline. At Visit 2, DCR and PFTs will be performed at the trough (24 hours after the last administration of T/O), and DCR, PFTs, CAT, Transition Dyspnoea Index (TDI) assessment and CT will be performed at the peak (2 hours 30 min post-inhalation of T/O) (figure 1).

This study was titled 'The efficacy of tiotropium and olodaterol combination therapy in COPD. Evaluation by dynamic chest radiography (EMBODY) study'.

Data collection

Dynamic chest radiography

Sequential chest radiographs will be obtained using a dynamic flat-panel detector (FPD) imaging system (Konica Minolta, Tokyo, Japan) composed of an FPD (Digital Radiography SKR 3000; Konica Minolta, Tokyo, Japan) and conventional radiography system with a pulsed X-ray generator (RADSpeed Pro; Shimadzu Corporation, Kyoto, Japan). DCR will be performed under conditions similar to those described in previous reports.[9 11 12] The following X-ray exposure parameters will be used: tube voltage, 100 kV; tube current, 80 mA; and pulse duration of pulsed X-ray, 4.0 to 8.0 ms (adjusted based on patient body mass index). The exposure time will be approximately 15 s. The pixel and matrix sizes will be 400 m × 400 m and 1062 m × 1062 m, respectively. Dynamic image data will be captured at a rate of 15 frames/s. The entrance surface dose will be adjusted by body mass index. DCR imaging will be performed with the patient in a standing position. For an accurate evaluation of pulmonary function, it is crucial to include one respiratory cycle within a limited amount of time with good reproducibility. It is recommended to use an automatic voice system and conduct pretraining for patients.[6] In the current study, a prerecorded voice will instruct the participants to inhale and exhale slowly, followed by maximal inhalation and exhalation each for 5 s, and to hold their breath for 2 s at each maximum inspiration and expiration point. All participants will rehearse before recording the DCR to ensure that instructions will be followed correctly.

Analysis of DCR images

Lung areas and diaphragmatic motion on sequential chest radiographs during forced breathing will be analysed using DI-X1 and prototype software (Konica Minolta, Tokyo, Japan). The lung areas at maximum inspiration (S_In) and maximum expiration (S_Ex) will be measured, as described elsewhere.[11] The Rs ratio is defined as the rate of change in the lung area due to respiratory motion from maximum inspiration to maximum expiration. The rate of change in the lung will be calculated as follows: Rs = (S_Ex − S_In)/S_In. The following definition of each measurable Rs will be used: Rs 1, Rs measured at Visit 1 (baseline); Rs 2, Rs measured at trough (Visit 2); and Rs 3, Rs measured at peak (Visit 2) (figure 1). Furthermore, the vertical excursions and motion speeds of the bilateral diaphragm will be calculated as described elsewhere.[9] The edges of the diaphragm on each dynamic chest radiograph will be automatically determined using edge detection. The highest points of the bilateral diaphragms will be automatically tracked using the template-matching technique throughout the respiratory phase, and the vertical excursions and motion speeds of the bilateral diaphragm will be calculated.

The tracheal diameter at maximum inspiration and maximum expiration will be analysed on the DCR images, as described elsewhere.[12] Tracheal diameters at the start of expiration and maximum expiration will be measured at the level of the intrathoracic trachea. Tracheal diameter change and narrowing rate (TNr) will be calculated as follows: tracheal diameter change=maximum tracheal diameter at the start of expiration − minimum tracheal diameter at maximum expiration and TNr=100 × (maximum tracheal diameter at the start of expiration − minimum tracheal diameter at maximum expiration)/maximum tracheal diameter at the start of expiration.

The MPCR will be analysed on DCR images, as described elsewhere.[16] The lung areas will be divided into small blocks of 5×5 pixels. The pixel value change rate of each small block during respiration will be calculated, and the MPCR will be detected during the inspiratory and expiratory phases; subsequently, the craniocaudal gradient of the MPCR will be calculated. Pulmonary ventilation and circulation will be assessed, as described elsewhere.[6] After image registration and noise reduction, the inter-frame differences in the pixel values of the low-frequency (ventilation) and high-frequency (perfusion) components will be calculated. Images of pulmonary ventilation and circulation will be created based on these calculations.

Pulmonary function tests

The PFTs will be performed using a CHESTAC-8900 spirometer (Chest M1, Tokyo, Japan). The helium dilution method for the calculation of the total lung volume, single breath method for assessing the diffusing capacity of the lung for carbon monoxide (DLco) and diffusing capacity of alveolar ventilation will be implemented. The following data will be measured: VC (vital capacity), %VC, FVC (forced vital capacity), %FVC, FEV_1, %FEV_1, FEV_1/FVC, the maximal flow rate of expiration at 50% (V_{50}) and 25% (V_{25}) of forced vital capacity, V_{50}/V_{25}, inspiratory capacity, FRC, %FRC, RV, %RV, RV/TLC, TLC (total lung capacity), %TLC, DLco, %DLco, DLco/alveolar volume (DLco/V_A), %DLco/V_A. All examinations and calculations will be performed in accordance with the guidelines of the Japanese Respiratory Society.[20]

CAT score

Participants' symptoms will be recorded using the CAT. This questionnaire consists of eight items scored on a scale ranging from 0 (no impairment) to 5 (very severe

impairment); the items are related to cough, sputum, chest tightness, breathlessness on hills/stairs, activity limitation at home, sleep and fatigue.[21] Elevated scores suggest a greater impact of COPD on the participants' symptoms.

BDI/TDI score

To evaluate the severity of the participants' breathlessness, the BDI at Visit 1 and TDI at the peak (Visit 2) will be measured. The BDI and TDI comprise three categories of functional impairment as well as the magnitude of task and effort.[22] Each category of the BDI has five severity grades, ranging from 0 (very severe impairment) to 4 (no impairment), and the scores of the three categories are summed to calculate the BDI score (0–12). The score of each category of TDI ranges from minus three (major deterioration) to plus three (major improvement) including a score of 0 to indicate 'no change'. The scores of the three categories are summed to calculate the TDI score, which will range from −9, including 0, to +9.[22]

Computed tomography

All patients will undergo a 64-MDCT scan (Revolution Maxima; GE Healthcare, Milwaukee, Wisconsin, USA) from the thoracic inlet to the diaphragm in full inspiration and expiration at Visit 1 and at peak at Visit 2. The following MDCT scan parameters will be used: collimation, 0.625 mm; automatic exposure control, 120 kV; gantry rotation time, 0.5 s; and pitch factor, 0.98. All images will be reconstructed using both a standard and bone-plus reconstruction algorithm with a slice thickness of 1.25 mm and reconstruction interval of 1.25 mm. Quantifiable CT parameters will be analysed using the Synapse Vincent image analysis system (Fujifilm, Tokyo, Japan) and ImageJ software (https://imagej.net/ij/). In addition, radiomics features including energy, entropy, uniformity, kurtosis, skewness and elongation will be analysed using Pyradiomics (https://pyradiomics.readthedocs.io/). Two pulmonologists blinded to all clinical information will independently review the data.

Participants

The EMBODY study population will include patients with COPD who regularly visit Chiba University Hospital. All patients will be required to provide written informed consent before participating in the study. Male or female patients with COPD, aged 40 years to 85 years, with a smoking history of more than 10 pack-years and an airway obstruction with post-bronchodilator FEV_1/FVC <70% and 30% ≤ FEV_1 <80% of predicted normal, who can perform forced breathing, rest breathing and breath holding in the standing position, will be included. The following exclusion criteria will be used. Patients with a diagnosis of asthma, tachycardia >100 beats per minute or life-threatening arrhythmia, obvious dementia, angle-closure glaucoma, dysuria due to benign prostatic hyperplasia, impaired mobility, including an impaired walking ability, due to limb dysfunction and bone fracture will be excluded. Patients with the following medical histories will also be excluded: asthma, acute exacerbation of COPD within 1 month, hospitalisation for heart failure within 1 year, acute myocardial infarction within 1 year, hypersensitivity to atropine and its related substances or components and cancer within 5 years (excluding basal cell carcinoma and squamous epithelial skin cancer and patients who underwent endoscopic mucosal resection of gastrointestinal tumours). However, in the case of cancer, the exclusion criteria will not apply to patients who are not expected to develop cancer recurrence requiring treatment during the study period, who have performance status 0 at the time of study registration per the discretion of a specialist, and who have no problem walking. Participants with significant mental health conditions, who are deemed by the investigator to be unable to complete study assessments, will be excluded. Additionally, patients who are not able to perform the PFTs properly (including those with a history of pulmonary resection) will be excluded. Moreover, we will exclude patients who do not understand the purpose and methodology of the study. We will also exclude patients who are judged to have difficulty with temporary suspension of medication when taking LAMA or LABA and who are deemed by the investigator to be unsuitable for the study. Finally, pregnant or lactating women and women who can become pregnant but cannot use contraceptives will be excluded.

Recruitment

Participants will be recruited through referral to Chiba University Hospital and will be screened for eligibility before study enrollment.

Interventions

Patients who consent to participate in the EMBODY study will be enrolled. Following an initial screening visit, patients will observe a 2–4 weeks washout period from any long-acting bronchodilators; subsequently, they will receive T/O for 6 weeks. The treatment will consist of the administration of a 5/5 µg inhalation solution of T/O (2.5/2.5 µg per actuation, two actuations per treatment) using the Respimat inhaler (Boehringer Ingelheim).

Procedure

Throughout the EMBODY study period, patients will self-administer the study drug by inhalation at home in the morning, and salbutamol or procaterol will also be permitted as rescue medication. Patients will be instructed to record the number of times they used the rescue medication and their use of the study drug in a diary. A rate of 50% or higher will be required for T/O compliance. Bronchodilators other than T/O, salbutamol and procaterol, will be discontinued throughout the study period.

If a patient uses inhaled corticosteroids, β blockers, and short-acting and long-acting xanthine derivatives before study enrolment, the same dose will be maintained throughout the study. At Visit 2, the patient will visit the hospital without using the medication and undergo DCR and PFTs (trough), after which the patient will inhale T/O. The patient will then undergo DCR, PFTs and CT, and PROs will be recorded 2 hours 30 min after inhalation (peak). When performing PFTs, rescue medications will be withdrawn on Visits 1 and 2. Short-acting and long-acting xanthine derivatives will be withdrawn 24 hours and 48 hours before Visit 1 and 2, respectively.

Primary outcome measures

The primary endpoint is the change in the Rs ratio between pre-therapy and post-therapy values (Rs 3 vs Rs 1, Rs 2 vs Rs 1 and Rs 3 vs Rs 2).

Secondary outcomes measures

Secondary endpoints include differences in other DCR parameters (diaphragm kinetics, tracheal diameter change and MPCR), PFT results and PROs between pre-therapy and post-therapy values. Clinical safety laboratory test results and adverse events will be recorded.

Additional outcomes measures

Additional endpoints include differences in the remaining DCR parameters (ventilation, perfusion, ventilation-perfusion mismatch) and CT indices between pre- and post-therapy values.

Data analysis

SAS software (SAS Institute, North Carolina, USA) will be used for statistical analyses.

Descriptive statistics will be calculated for the basic characteristics of the study participants (background patient characteristics). Descriptive statistics for continuous variables will be expressed as the mean, SD, range and IQR. Descriptive statistics for categorical variables will be calculated as frequencies and percentages. For the primary analysis, we will estimate the change between pre-therapy and post-therapy Rs to analyse the treatment effects. The comparison will be performed using a paired t-test and an estimation of the difference between pre-therapy and post-therapy values and its 95% CI. Secondary analysis will be performed using statistics similar to those in the primary analysis to supplement the results of the primary analysis. Depending on the characteristics of the variables, a signed rank-sum test (signed rank test) will be used in addition to the paired t-test for the one sample mean. If necessary, correlation coefficients, multiple regression analyses, and independent two-sample comparisons will be performed before and after therapy. The statistical significance level will be set at $p<0.05$, and two-sided 95% CIs will be calculated.

Sample size calculation

We set the conditions for two-sided statistical analyses at an examination power of 80% and a significance probability of 5%. The effect size was calculated in a previous study based on the effects of T/O on RV response at 2 hours 30 min post dose[2] and on the association between the Rs ratio and RV/TLC ratio.[11] We assumed that the Rs for the placebo and T/O were −0.18±0.061 (Rs P) and −0.228±0.061 (RS Tx), respectively. We assumed Rs 1 to be Rs P and Rs 3 to be RS Tx to calculate the sample size. As this primary outcome is a new indicator, the required sample size was calculated using the Wilcoxon signed-rank test with an almost independent pretreatment and post-treatment correlation of 0.1 as a robust model for the paired t-test. The sample size was calculated as 28. Considering a 20% dropout rate, the required sample size was determined to be 35.

Patient and public involvement

This trial will not involve patient representatives in the development of the EMBODY study design or recruitment of participants. The results of the trial will be presented at national and international meetings and will be published in peer-reviewed journals.

Strengths and limitations

The strength of the EMBODY study lies in its introduction of novel information such as (1) the effectiveness of DCR in assessing the respiratory kinetic effect of bronchodilators in patients with moderate-to-severe COPD, (2) the association between DCR parameters, PFT results and PROs in the context of bronchodilator therapy and (3) the influence of bronchodilators on the amelioration of RV in patients with COPD in Japan.

The limitations of this study are as follows: as this will be a single-centre, non-controlled study with a relatively small number of participants, which makes it more prone to selection and intervention-related bias, the generalisability of the study findings to other populations can be restricted. Since the main purpose of this study is to collect information on the usefulness of DCR as a new modality, we decided to conduct a non-controlled, comparative study and perform a pretreatment and post-treatment comparison (paired t-test). Once the usefulness of DCR has been demonstrated, measures such as stratification by background, including baseline lung function and treatment, may need to be considered when conducting large-scale comparative trials.

In addition, it may be desirable to conduct the DCR multiple times per measure to account for variations. However, a previous study that analysed DCR variations in patients with interstitial lung disease has demonstrated the reproducibility of DCR by using an automatic voice system and conducting pretraining for patients.[23] By using an automatic voice and pretraining, we decided to perform a single

measurement to reduce radiation exposure by DCR. Despite these important limitations, this study could provide additional evidence for the potential of DCR in guiding COPD therapy.

ETHICS AND DISSEMINATION

The EMBODY study will be performed in conformity with the principles of the Declaration of Helsinki and the Harmonised Tripartite Guidelines for Good Clinical Practice of the International Conference on Harmonisation. Written informed consent will be obtained from all patients. Ethical approval for the study has been obtained from the Ethics Committee of Chiba University Hospital, Chiba, Japan (CRB0051-21). This study has been registered with the Japan Registry of Clinical Trials. The results of the trial will be presented at national and international meetings and published in peer-reviewed journals for further dissemination.

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Collaborators Not applicable.

Contributors Trial concept and design: JI, SS, KT and TS. Acquisition of data: JI, MK, AU, TI, YS, EA, TK, SF, KOku, JO, ES, YM and KM. Analysis and interpretation of data: JI, AN, HY, KOno, KOka, KOku, NK and YO. Drafting the article: JI, YO, KM, SS, TU, KT and TS. JI is the guarantor. All authors contributed to revising it critically for important intellectual content and final approval of the version to be published. JI had full access to all trial data and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Competing interests KOno and KOka is currently employed full-time at KonicaMinolta.inc. None of the other authors declare any competing interests.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Ethical approval for the study has been obtained from the Ethics Committee of Chiba University Hospital, Chiba, Japan (CRB0051-21). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data are available upon reasonable request from the corresponding author.

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