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Study Protocol

Development of Integrative Medicine Therapy for Gastrointestinal Autoimmune Diseases: A study protocol for a registry study

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ABSTRACT

Background: Although the incidence of AD, including gastrointestinal AD, increases every year, there is no effective therapy for it yet. This causes high medical costs to be spent on the management of autoimmune patients every year. The aim of this study is to identify the characteristics related to the causes and symptoms of gastrointestinal autoimmune disease (AD) by collecting patients' information and to further contribute to the development of an integrative medicine therapy for gastrointestinal AD.
Methods/design: This study is a registry study of patients diagnosed with gastrointestinal AD. Subjects who voluntarily sign a written consent form after receiving a sufficient explanation will be assessed for compliance with the inclusion and exclusion criteria through a screening process on their first visit. A total of 35 subjects will be recruited; 15 will be assigned to the patient group, 10 to the control group, 8 to the caregiver group, and 2 to the medical staff group. The clinical information of the subjects will be evaluated through statistical analyses. As this study is a registry study, it will not test specific hypotheses.
Discussion: If this study identifies the significant characteristics of gastrointestinal AD patients, the results will be useful for the development of integrative medicine methods for the treatment of gastrointestinal AD.
Study registration: This study was registered with the Clinical Research Information Service (CRIS) of the Korea National Institute of Health (NIH), Republic of Korea (KCT0003976, date of registration: May 23, 2019).

1. Introduction

Autoimmune disease (AD) is a disease that is caused by the balance disruption of the immune system and often progresses chronically.[1] The world incidence and prevalence of AD have been increasing by 19.1% and 12.5%, respectively, per year.[2] The net percentage increase in gastrointestinal AD ranks third among all Ads.[2] Although the incidence of gastrointestinal AD increases every year, there is no effective therapy for it yet.[1] In the United States, 100 billion health care dollars are spent on the management of autoimmune patients per year.[1] Therefore, new effective approaches are required to treat incurable diseases such as AD, and big data analyses may be a candidate approach.[3] Recently, big data analysis has become one of the most notable approaches in many fields.[4,5] In particular, the integrative analysis of clinical big data increases the feasibility of precision medicine.[4] In fact, many researchers are using big data analyses to characterize incurable diseases.[4,6,7]

This study is a registry study that will collect and register the clinical information of gastrointestinal AD patients. The aim of this study is to identify the characteristics related to the causes and symptoms of gastrointestinal autoimmune disease (AD) by collecting patients' information and to further contribute to the development of an integrative medicine therapy for gastrointestinal AD. To achieve this goal we will obtain basic data through an analysis of metabolites using blood samples and an analysis of intestinal microorganisms using stool samples. Recently, metabo-

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lite and intestinal microorganisms analyses have become actively used for the development of incurable disease treatments.[8] In particular, microorganisms have been suggested as the basis that integrative treatment can be more effective than conventional treatment.[9] And several studies[10,11] have reported that intestinal microorganisms interact with herbal medicines. Considering these existing studies, if specific findings of intestinal microorganisms were observed in gastrointestinal AD patients, this study could be helpful for the development of integrative treatment using conventional treatment and herbal medicine.

2. Methods

2.1. Study registration

This study was registered with the Clinical Research Information Service (CRIS) of the Korea National Institute of Health (NIH), Republic of Korea (KCT0003976).

2.2. Study design

This study is a registry study of patients diagnosed with gastrointestinal AD. Subjects who voluntarily sign a written consent form after receiving a sufficient explanation will be evaluated for compliance with the inclusion and exclusion criteria through a screening process on their first visit. The subjects meeting the inclusion criteria will be assigned to the patient group. The control group will be a group of subjects from the general population who match the sex and age of the patient group for comparative analysis of the metabolite characteristics. In order to approach gastrointestinal AD in an integrative way and to analyze family epidemiology, patients' caregivers and medical staffs will also be included in this study.

The data to be collected for this study are as follows.

Patient group: Basic medical information, intestinal microbial analysis information, metabolic analysis information and information about the disease experience (through a qualitative interview).

Control group: Metabolic analysis information

Caregiver group: Information about the disease experience (through a qualitative interview)

Medical staff group: Information about the disease treatment experience (through a qualitative interview).

2.2.1. Study period

From December 10, 2018 to June 9, 2020 (However, the period can be extended if the patient recruitment is not completed.).

2.2.2. Name and address of study institute

St. Carollo General Hospital; 221, Sungwang-ro, Suncheon-si, Jeollanam-do, 57931, Republic of Korea, Tel) +82-61- 720-2123.

Wonkwang University, Gwangju medical center; 1140-23, Hoejae-or, Nam-gu, Gwangju, 61729, Republic of Korea Tel) +82-62-670-6700.

2.2.3. Name, title and affiliation of chief of research

Do-hyeon Kim (MD), Dept. of digestive internal medicine, St. Carollo General Hospital

2.3. Inclusion and exclusion criteria

2.3.1. Included diseases

Digestive autoimmune diseases according to the Korean standard classification of disease and cause of death (KCD) criteria:

Crohn's disease (KCD codes K50, K50.0, K50.00, K50.01, K50.02)

Ulcerative colitis (KCD codes K51, K51.8)

Behcet's disease (KCD codes M35.2, M35.20, M35.21, M35.22, M35.38)

Autoimmune hepatitis (KCD code K75.4)

Ulcerative (chronic) proctitis (KCD code K51.2)

2.3.2. Inclusion criteria

2.3.2.1. Patient group. Adults men and women aged 19–85 years who have been diagnosed with one of the following according to the KCD criteria: Crohn's disease, ulcerative colitis, Behcet's disease, autoimmune hepatitis, ulcerative (chronic) proctitis.

Those who can communicate sufficiently with the examiner and undergo a questionnaire and a qualitative (in-depth) interview.

Those who can be followed-up during the study.

Those who agree to participate and voluntarily sign the written consent form after receiving a sufficient explanation of the purpose and characteristics of the clinical study.

2.3.2.2. Control group. Those who have the same sex and age as the patients group subjects.

Those who have not been diagnosed with the disease.

Those who can be followed-up during the study.

Those who agree to participate and voluntarily sign the written consent form after receiving a sufficient explanation of the purpose and characteristics of the clinical study.

2.3.2.3. Medical staff group. Those who have a doctor or Korean medicine doctor license.

Those who have experience of treating patients with gastrointestinal AD.

Those who can communicate sufficiently with the examiner and undergo a questionnaire and a qualitative (in-depth) interview.

Those who can be followed-up during the study.

Those who agree to participate and voluntarily sign the written consent form after receiving a sufficient explanation of the purpose and characteristics of the clinical study.

2.3.2.4. Caregiver group. Those who care for gastrointestinal AD patients (not limited to family).

Those who can communicate sufficiently with the examiner and undergo a questionnaire and a qualitative (in-depth) interview.

Those who can be followed-up during the study.

Those who agree to participate and voluntarily sign the written consent form after receiving a sufficient explanation of the purpose and characteristics of the clinical study.

2.3.3. Exclusion criteria for patients, control, medical staff and caregiver group

Those who can't communicate normally.

Those who refuse to participate in the study or to provide their consent.

Those who lack the ability to understand or express themselves in Korean.

Those judged to be inadequate for the study by the medical staff.

Any other person deemed inadequate by the medical staff.

2.3.4. Early termination and dropout criteria

If a significant violation of the clinical research plan, such as the subject's misalignment with the inclusion and exclusion criteria, is found during the study.

If the subject or caregiver requests to stop the examination or withdraws their participation agreement during the study.

If the chief of research or a study researcher seriously violates the clinical research plan.

If the chief of research or a study researcher judges that the progress of the study is not appropriate.

Table 1
Assignment of subjects. 15 belonging to the patient group, 10 to the control group, 8 to the caregiver group, and 2 to the medical staff group.

	Patient group	Control group	Caregiver group	Medical staff group
Clinical information collection (number of people)	15	–	–	–
Qualitative interview(number of people)	8	–	8	2
Metabolic analysis information collection (number of people)	15	10	–	–

2.3.5. Process in case of early termination and dropout

If a subject is dropped out during the study, the researchers should stop the study and should record all the data obtained up to the dropout point, as well as the date of final treatment, the dropout date, the reasons for the dropout, and the dropout process.

2.4. Sample size and basis for calculation

Since this study is a registry study that will not test specific hypotheses, no sample size calculation is required. Therefore, since only the minimum number of samples (10 per group) need to be satisfied for the statistics, the initial set of patient and control group was 10 subjects, respectively. However, the number of patients group was increased by 5 to gather more gastrointestinal AD related data.

Two hospitals will collect the clinical information and qualitative interview data from a total of 35 subjects (Table 1). Among the 35 subjects, the patient group will be limited to those who have selectively agreed to provide three types of information. The subjects will be registered at the St. Carollo General Hospital and the Wonkwang University, Gwangju Medical Center according to their subject registration status. Caregiver of the patient who agreed to the qualitative interview is assigned to the caregiver group. One medical doctor and one traditional Korean medical doctor who treat gastrointestinal AD will be assigned to the medical staff group and will participate in the qualitative interview. The reason for recruiting caregivers and medical staffs is to enable the development of integrative treatment by collecting information not only of patients but also of the caregivers and doctors who treat them through qualitative interviews with them. Members of the general population of the same sex and age as the patient group who agree to provide metabolic analysis information will be assigned to the control group.

2.5. Plan for recruitment of study participants

2.5.1. Recruitment of patient group

Patients who visit the hospital for medical treatment will become candidates for the patient group recruitment.

2.5.2. Recruitment of control group

Subjects will be recruited through snowball sampling. No recruitment announcement will be issued, as the recruitment numbers are low. The sex and age of the control group members should be the same as those of the patient group members.

2.5.3. Recruitment of caregiver group

The caregivers of the patients who visit the hospital for medical treatment will become candidates for the caregiver group recruitment.

2.5.4. Recruitment of medical staff group

Medical staffs will be recruited through convenience sampling. No recruitment announcements will be issued, as the recruitment numbers are low (one medical doctor and one traditional Korean medical doctor).

2.6. Registration of subjects

2.6.1. Registration of patient group

Gastrointestinal AD patients who meet the inclusion and exclusion criteria will be assigned to the patient group. As this study is a registry study designed to register the information collected during gastrointestinal AD patients' medical treatment, the subjects will not be randomly assigned to groups.

2.6.2. Registration of control group

In this study, a control group is needed to compare the metabolite information collected through metabolite analyses using blood samples and stool with that of the patient group. Therefore, the control group will be composed of healthy people who are not ill (i.e., who have not been diagnosed with a specific disease over the past 3 months) in consideration of the patient group's sex and age ratio.

2.6.3. Registration of caregiver group

In this study, the caregivers of the patients participating in the qualitative interview will be recruited and enrolled in the caregiver group.

2.6.4. Registration of medical staff group

In this study, medical staff will be recruited and registered for qualitative interviews.

2.6.5. Registration items and methods

2.6.5.1. Progress of study. The course of all study will follow the planned time schedule of study (Table 2). However, if subjects are unable to visit due to unavoidable circumstances, the reason will need to be documented.

2.6.5.2. Basic information.

2.6.5.2.1. Subjects' consent and socio-demographic survey. Before beginning the study, the purpose and contents of the study should be explained in detail to the subjects and their written consent should be obtained. After investigating the socio-demographic information, the following must be recorded in the case report form (CRF): the subject's written consent, date of consent, initials, sex, date of birth, etc.

2.6.5.2.2. Investigation of disease and drug history. The past medical history of the last 3 years, including surgery, allergies, drug, etc., and the current medical history, including the name of the diagnosis, date of onset, date of first treatment, treatment duration, number of hospitalizations, opinion of the researcher, etc., should be recorded.

2.6.5.3. Clinical information.

2.6.5.3.1. Blood test.

- General blood test: CBC with differential cell count (WBC, RBC, HGB, HCT, PLT, neutrophil, lymphocyte, monocyte, eosinophil, and basophil).
- General chemical test: glucose, BUN, creatinine, cholesterol, total protein, albumin, AST, ALT, ALP, r-GTP, total bilirubin, Na, K, and CL.

Table 2
Time schedule of study. Allows ±7days from the specified date. If the subject and the qualitative research team agree, visits 1 and 2 can be carried out at once. Visit 2 will be conducted within ±7 days of visit 1. The qualitative interviewer and the researchers must specify the date and location by contacting the interviewees individually.

Study schedule	Screening	Visit 1	Visit 2 (1week ± 7days)
Visit date confirmation	●		
Acquisition of subject's consent	●		
Subject numbering	●		
Socio-demographic survey	●		
Investigation of drug history	●		
Investigation of disease history	●		
Investigation of drinking and smoking history	●		
Subject compatibility evaluation(inclusion/exclusion criteria apply)	●		
Vital signs confirmation	●	●	●
Blood tests		●	
Examination of intestinal microorganism and blood metabolites		●	
Psychological tests(quality of life and simple mental health questionnaire)			●
Qualitative interview			●
Adverse events collection		●	●
End of test			●

- Quality of life test (Short Form Health Survey-36): measuring physical functioning, social functioning, role limitation due to physical and emotional health problems, mental health, vitality, bodily pain, general health perceptions, and changes in health status.
- Abbreviated simple psychiatric test (Brief Symptom Inventory 18): measuring somatization symptoms, depression, and anxiety.

2.6.5.4. Analysis of intestinal microbes and blood metabolites.

2.6.5.4.1. Blood collection method. After collecting 5 ml of blood using the injection needle provided in the blood collection KIT, the blood will be divided into 3.0 ml and 2.0 ml and will be packed in serum separate tube (SST) and nonautologous-pooled human plasma (NAHP) containers, respectively. The serum and plasma will then be separated.

2.6.5.4.2. Blood analysis.

1) Blood analysis standards: WBC, RBC, platelets, and other factors commonly used as indicators and metabolites will be used as indicators in this blood analysis. For the matabolites, the peak values will be analyzed and the results will be presented without specifying and searching for these indicators in advance.
2) Blood analysis and storage after collection in the diagnostic laboratory (refrigerator & cryocooler).
3) Transfer the specimens (approx. 500 μL) from the diagnostic laboratory to the analytical laboratory for analysis.
4) The analytical institution will use EIA and metabolomic tools to identify the biomarkers in the blood.

2.6.5.4.3. Intestinal microbial analysis and stool collection methods.

1) Meal adjustment guide: The subjects will be instructed not to drink alcohol or to eat excessively fatty foods the day before the stool collection.
2) Stool collection and specimen delivery: 4 mg of stool will be sealed in a KIT for stool collection; the outside of the KIT will be labelled so that the subjects' specimens can be distinguished. The specimens will then be frozen at −20 ° and will be delivered to the analytical laboratory.
3) Intestinal microbial analysis: The analytical laboratory will analyze the specimens to identify the microorganisms according to the institution's protocol.

2.6.5.4.4. Sample processing.

1) At the end of the clinical study, the analytical institute will collectively dispose of the samples through designated companies.
2) If the subject's consent is withdrawn, the samples shall also be disposed of.

2.6.5.5. Qualitative interview on disease experience.

1) Semi-structured questionnaires will be used to conduct in-depth interviews of the patients and their families on their disease experiences. Question contents: early onset perception, medical treatment experience, traditional Korean medical treatment experience, advantages and disadvantages of the medical and traditional Korean medical treatment processes, alternative therapy experience, need for integrative treatment (qualitative interview questionnaire attached).
2) Semi-structured questionnaires will be used to conduct in-depth interviews of the medical staff about their experiences treating patients with gastrointestinal AD.
3) All of these qualitative interviews were conducted by a professional researcher with a doctor's degree in Counseling Psychology.

2.6.5.6. Adverse events. The subjects should be trained to voluntarily report adverse events (AEs) to the researcher, and the researcher should check for them at each regular or additional visit through a consultation. The AE investigation should include the onset date, disappearance date, degree and result of the AEs, the actions taken in relation to the study, the causal relationships with the study, other suspected medication names, whether and how to treat the AEs, etc.

2.6.5.7. Combination drugs and treatments, prohibited drugs and treatments. As this is a registry study, there is no drug restriction for treatment.

2.6.5.8. Process in case of protocol violations. The researcher performing this study should be well-informed of and should thoroughly follow the protocol to avoid protocol violations. Appropriate measures should be taken to allow the subjects to visit on specified dates.

In the event of violation of a critical study protocol, the subject should be excluded from the analysis (excluding from the PP) in principle. Critical violations are as follows:

Consent has not been received.

The inclusion/exclusion criteria have been violated.

Key tests at the beginning and end of the study have been missed.

Other minor violations of the study protocol that are considered to have no effect on the interpretation of the study results should be clearly documented in terms of extent and reason. Moreover, a comprehensive review of whether the violations affected the study must be included in the PP analysis.

2.6.5.9. Monitoring. As this study is a registry study, no further monitoring will be needed.

2.6.5.10. Inspection and survey. Ensure that this study has been performed in accordance with the protocol and standard work instructions. If any problems, such as non-conformity, errors, etc., are confirmed by the inspection according to the management standard of protocol for a study, they must be supplemented by appropriate measures. In response to a request from the Ministry of Food and Drug Safety (MFDS), the chief of research and the researchers will be assessed for their reliability at an appropriate time after the end of the study.

2.6.5.11. Archiving and reading of materials. The chief of the study institute, chief of the committee, and chief of research should keep the records and data from the judging committee's screening and the various data related to the protocol, the subjects' consent, and the study process for three years. However, if archiving of more than three years is required and the chief of the study institute agrees, the archiving period can be extended. If the sponsor decides that it is no longer necessary to archive the data, they should communicate this information in a document and should notify the chief of the study institute. The chief of research should archive the basic documentation and the study documentation, and must ensure that these documents are not prematurely damaged or lost by accident. After completion of the final report, these documents should be handed over to the specified director in charge of archiving at the study institute. At the request of the MFDS, the chief of research should be able to provide or view the relevant documents under the subjects' confidentiality conditions.

2.7. Table of study schedule

Table 2.

2.8. Statistical analysis

2.8.1. General principles of statistical analysis

This study is a registry study that will collect the clinical information of patients with gastrointestinal AD and will accumulate qualitative data through in-depth interviews, without testing specific hypotheses.

Continuous variables will be expressed as means (standard deviations) or medians (quartiles).

Categorical variables will be expressed as numbers and percentages of patients.

The incidence of clinical events will be expressed as a percentage (number of cases) or a cumulative incidence.

Except for qualitative data, the data obtained from the subjects will be analyzed with the SPSS for Windows (ver 20.0) statistical package program after coding.

2.8.2. Correlation analysis of registration data

To analyze the correlations between the variables, a Pearson product-moment correlation analysis will be used for continuous variables, and a Spearman correlation analysis for ordinal variables.

2.8.3. Metabolic analysis

A test of normality will be conducted to compare the metabolic analyses of the patient and control groups. A two-sample *t*-test will be used when the data are normally distributed, and a Mann-Whitney *U* test when the data are not normally distributed.

2.8.4. Qualitative interview materials

The qualitative interview data will be analyzed with the applied grounded theory qualitative analysis method. The validity of the results of the qualitative interview data analysis will be verified through cross-validation by experts.

2.9. Predicted adverse events

This study is expected to have no AE since it is a patient registry study in which no special treatment will be added. However, it is believed that there will be a minimum risk of invasive activity when conducting the blood tests. If side effects such as unexpected bleeding or ecchymosis occur during a blood test and additional expenses are incurred, the study institute should bear the burden.

2.10. Ethics and dissemination

2.10.1. Ethical approval

This study has been approved by the Institutional review Board (IRB) of the Wonkwang University Gwangju Hospital, Gwangju, Republic of Korea (SCH2018-0116).

2.10.2. Consent statement and written consent

Studies can only begin if the subjects voluntarily sign an agreement to participate in the studies after hearing a full description of the purpose, possible AEs, and safety of the studies. If a subject or legal representative cannot read the consent form, the subject manual, or any other documented information, a fair entrant will attend the entire process of obtaining consent. In this case, the documented information should be read and explained to the subject or their legal representative, and they should verbally agree to participate in the study, and, if possible, should sign the consent form and record the date themselves. The fair entrant should ensure that the process of the subject or legal representative receiving sufficient explanation and agreeing to participate in the clinical study is carried out in respect of their free will.

2.10.3. Victims compensation covenant

As this study is a registry study without intervention, no harm such as immediate side effects is expected. However, in case of emergency, a victim compensation regulation should be prepared separately and the victim should be provided the best possible treatment.

2.10.4. Helsinki declaration and good clinical practice compliance

This study will be conducted in compliance with ethical principles based on the "Helsinki Declaration" and the "Good Clinical Practice (GCP)" and will protect the human rights, welfare, and safety of the subjects.

2.10.5. Confidentiality of subjects

Records to identify the subjects will be kept confidential. While the information, data, and results of the studies may be presented for academic purposes and other purposes, the identity of the subjects must remain confidential. The details are as follows.

The sponsor and monitor involved in this study can view the subjects' records to monitor and control the progress of the study. By signing this proposal, the researchers acknowledge that, in accordance with national legislation and ethics, the study sponsor or monitor from the contract research organization (CRO) may

review or copy the documents or verify the subjects' medical records and CRF records.

Such information should be kept confidential, and facilities and standards for confidentiality should be maintained.

All documents related to studies, such as CRFs, should be recorded and identified with the subject's identification code (usually the subject's initials), not the subject's name.

The signed consent should be kept by the chief of research during the study period. When the study is over, it must be transferred to the IRB committee of the affiliated hospital to be stored and then discarded. The researcher should make a list of the subjects' numbers and names to help find the records in the future.

2.10.6. Measures to protect subjects' safety

The researchers should be thoroughly aware of the side effects and precautions specified in the protocol. If an SAE occurs during a study, they must immediately stop the study for the subject, take appropriate measures, and notify the IRB committee of the facts.

2.10.7. Protection measures for vulnerable subjects

Vulnerable subjects are those who have a high expectation or interest in participating in study, or who are concerned about the disadvantages to be received from senior supporters when they refuse to participate (e.g., students from medical colleges, traditional Korean medicine colleges, dental colleges, pharmacy colleges, or nursing colleges, workers at medical institutions or laboratories, pharmaceutical company employees, soldiers, etc.), those who are afflicted with incurable diseases, those who are accommodated in collective facilities, poor people, emergency patients, minority races, homeless people, refugees, minors, and those who cannot agree of their free will.

Employees of medical institutions and laboratories, the unemployed, the poor, and those aged 65 or older can participate in this study. The researcher will not engage in any incentivization to recruit them and will allow participation if they are willing to participate, to the extent that their rights and welfare are protected. There will be a separate statement for elderly people over 65 years of age, and in order to reaffirm their voluntary intention, the subjects will need to sign a consent form that will state, "I will voluntarily participate in this study." (However, if the IRB committee permits it, separate statements for elderly people over 65 years of age can be substituted for the same explanation and consent form as for the general subjects).

2.10.8. Changes to study protocol

Any changes to the protocol that may affect the performance of the study, its benefits, or the safety of the subjects—including changes to the purpose of the study, the study design, the sample size, the study procedures, etc.—will require a formal protocol change. These changes should be approved by the IRB committee before implementation.

2.10.9. Records and management of study data

The data management of this study should be carried out in accordance with the latest standardized working guidelines of the affiliated hospitals' medical device study centers. Matters not specified in this protocol and in standard work guidelines should be implemented in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)-GCP.

1) CRF writing and source document verification

- A CRE or electronic CRF (eCRF) should be filled out immediately whenever any material needs to be entered. If it is not recorded until the end of the case, the reason for the omission should be recorded.

- Modifications to all data obtained through the studies should be marked on a single line so that the previous record is visible, and the modification data, the modifier, the reason for the modification, and the modification date should be recorded. A correction fluid should not be used in order to keep the first record visible. On electronic documents, the original data, the modifier, the reason for the modification, and the modification data should be recorded as data.

- Writing in the CRF should follow the affiliated hospitals' standard operating procedure (SOP).

2) Data entry

- If no eCRF is used, data can be entered using Excel, etc. The data entry person must be appointed by the chief of research.

3) Archiving of CRF

- After the data has been entered into the computer, the source document, the CRF, and the eCRF database should be kept so that they can be verified by the relevant government agencies, the judging committee, etc. When a study is finished, the data from the study must be kept as a file on CD, DVD, or other storage media, independently from the entire backup process of the medical device study center computer system.

2.10.10. Storage and disposal of study samples

The results of the subjects' blood sample tests taken for this study should only be used for the purposes of this study. The samples should be kept for 2 years after the test. After completion of the study, they should be discarded according to the relevant procedures of the analytical laboratory (the relevant detailed procedures follow the SOP of each executing agency). The subjects' samples or results will not be sold, loaned, or donated to an independent third party for other purposes, and no individual genetic information will be extracted from the blood samples. If a study is terminated abnormally due to consent withdrawal or other causes, the blood samples and information extracted from them must immediately be discarded.

3. Discussion

The incidence of AD has been increasing every year.[2] Despite this progression, no clear treatment has been found. This represents an important global problem.[1] A new approach is needed to solve this problem, and the use of big data can offer an alternative.[3] Big data is characterized by three Vs: volume, which refers to the large size of the data; velocity, which refers to the high speed at which the data are generated; and variety, which refers to the heterogeneity of the data coming from different sources.[8] An integrative approach based on this big data can increase the feasibility of precision medicine.[8]

This study will take the first step toward an integrative analysis of big data for the development of integrative medicine treatment methods for gastrointestinal AD. It will collect, register, and analyze the clinical information of gastrointestinal AD patients (basic information, intestinal microbial and metabolic analysis information, and qualitative date on disease experience) to identify the characteristics of gastrointestinal AD. Those who do not meet the exclusion criteria but who meet the selection criteria will be assigned to the patient group, and members of the general population matching the sex and age of the patient group members will be assigned to the control group. For family epidemiology analysis, caregivers of subjects in the patient group and medical staff who treat patients will also be included in the study. Correlation analyses, metabolism analyses, and qualitative analyses will be conducted according to the registered data type. Although the number of subjects in this study is not large, if significant characteristics of gastrointestinal AD patients and healthy people are found in this study, it will be possible to carry out large-scale studies in the future, and the big data obtained from that study will be useful

for the development of integrative medicine treatment methods for gastrointestinal AD.

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Author's contribution

CHK and KKS designed and drafted the protocol and manuscript. DHK, YJM, and HRS examined the inclusion criteria in clinical practice. HC and GHK critically revised the manuscript. SL organized all procedures and revised the protocol. All authors have read and approved the final manuscript.

Conflicts of interest

The authors declare that there is no conflict of interest.

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Ethical statement

This study has been approved by the Institutional review Board (IRB) of the Wonkwang University Gwangju Hospital, Gwangju, Republic of Korea (SCH2018-0116, date of approval: December 10, 2018).

Data availability

The data of this study will be kindly provided when requested through the corresponding author's e-mail.

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