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Protocol of a randomised controlled trial assessing the impact of physical activity on bone health in children with inflammatory bowel disease

Jérémy Vanhelst [ORCID],[1] Stéphanie Coopman,[2] Julien Labreuche,[3] Claire Dupont,[4] Valérie Bertrand,[5] Djamal Djeddi,[6] Dominique Turck,[1,2] Delphine Ley[1,2]

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For numbered affiliations see end of article.

Correspondence to
Dr Jérémy Vanhelst;
jeremy.vanhelst@chru-lille.fr

ABSTRACT

Introduction Low bone mineral density (BMD) is a frequent issue in children and adolescents with inflammatory bowel disease (IBD). Several studies in healthy populations have reported a positive impact of physical activity (PA) on bone health. Recently, an observational study in paediatric patients with IBD showed a significant positive relationship between daily PA and BMD. However, intervention studies investigating a causal relationship between PA and BMD are warranted to confirm these results. The aim of this randomised controlled trial will be to investigate the effect of a PA programme on BMD in paediatric patients with IBD.

Methods and analysis This trial is a multicentre (four centres), randomised, controlled, blinded end-point study. Eighty children with IBD will be randomly assigned in a 1:1 ratio to receive a programme with adapted physical exercises (intervention group) or usual PA (control group) during a 9-month period. The primary outcome is the change from baseline at 9 months (the end of the study) in whole-body BMD assessed by dual-energy X-ray absorptiometry. Secondary efficacy outcomes include the changes from baseline at 9 months in: BMD assessed in the lumbar spine and trochanter; daily PA (time spent in moderate-to-vigorous PA); body composition (fat mass and fat-free mass); fatigue resistance; quality of life and activity of IBD.

Ethics and dissemination The study was approved by the Research Ethics Committee in France (Comité de Protection des Personnes, Sud-Ouest and Outre-Mer III, Bordeaux, France, No 2018/27). All procedures will be performed according to the ethical standards of the Helsinki Declaration of 1975, as revised in 2008, and the European Union's Guidelines for Good Clinical Practice. Written informed consent will be obtained from the parents or legal guardian and from the children. Research findings will be disseminated in peer-reviewed journals and scientific meetings.

Trial registration number NCT03774329.

Strengths and limitations of this study

► This is a multicentre, randomised, controlled, blinded end-point study testing the efficacy of a physical activity (PA) training programme during a consecutive 9-month period in paediatric patients with inflammatory bowel disease (IBD).
► This is the first randomised study to assess the impact of a PA programme involving weight-bearing to improve bone health in children with IBD.
► Gold standard objective methods will be used to assess both PA (using accelerometry) and bone health (using dual-energy X-ray absorptiometry).
► Although this a multicentre, randomised, controlled study, results obtained in this trial will not allow for comparison with patients with Crohn's disease or ulcerative colitis due to a small sample size.
► A potential limitation of the present protocol is the home-based PA programme with the risk of lower compliance throughout the 9-month PA training period.

(UC) and IBD-unclassified (IBD-U), is characterised by chronic inflammation of the gastrointestinal tract. The incidence of IBD has substantially increased over the last 50 years in the Western world. As an example, during the last two decades, the incidence of IBD has increased dramatically among teenagers in Northern France, with an increase in 126% and 156% for CD and UC, respectively.[1] At the turn of the 21st century, IBD has become a global disease in newly industrialised countries whose societies have become more westernised.[2]

Bone health is a major concern in IBD

Osteoporosis is a skeletal disease characterised by low bone mineral density (BMD) and a high risk of fracture and is associated with high morbidity and mortality in adulthood.[3] It is a major public health concern worldwide. Bone mass acquisition during childhood and

INTRODUCTION

Dramatic increase in the incidence of inflammatory bowel disease

Inflammatory bowel disease (IBD), consisting of Crohn's disease (CD), ulcerative colitis

adolescence is a major determinant of skeletal health during later life.[4] Growth failure associated with low BMD is a common complication in paediatric IBD. The prevalence of low BMD in children and adolescents with IBD ranges from 8% to 65%.[5–8] BMD abnormalities in IBD are associated with the use of corticosteroids, disease activity, low body weight, young age at onset, pubertal delay, vitamin D deficiency, low calcium intake and intestinal malabsorption.[9–11]

Daily physical activity and IBD

Physical activity (PA) is recognised as an important determinant of health in children and adolescents. Increasing participation in moderate-to-vigorous PA (MVPA) has important health benefits such as decreased risk for obesity, cardiovascular and pulmonary diseases, cancer, depression as well as better bone health.[12] Physical inactivity in children and adolescents is associated with low physical abilities and increased morbidity and mortality in adulthood.[13] Some health benefits occur immediately after an episode of PA. Other benefits begin with as little as 60 min/day; it has been shown that 60 min a day of MVPA consistently reduces the risk of many chronic diseases and other adverse health outcomes.[14] However, a recent systematic review showed that data on PA in children and adolescents with IBD are scarce, with only five studies published over the last decade.[15–17] Ploeger et al[16] assessed the response of inflammatory cells and cytokines to acute bouts of moderate-intensity continuous exercise and high-intensity intermittent exercise in youth with CD and in healthy matched controls. They concluded that moderate PA of short duration is not associated with significant exacerbation of inflammation.[16] Three studies compared PA levels and sedentary time in paediatric patients with IBD and in healthy controls.[18–20] The conclusions from these studies were as follows: (1) children with active disease had a lower PA level than children in remission, (2) sedentary time or prevalence of television (TV) watching and computer or video game usage (all activities combined) was similar between children with IBD and controls and (3) although the differences in PA duration and number of steps between paediatric patients with IBD and healthy controls did not reach statistical significance, female patients had a significantly shorter duration of total and moderate-intensity PA.

Daily PA, a PA programme and bone health

Many animal studies have assessed the osteogenic response (ie, bone formation) to a PA programme and demonstrated that mechanical stress (ie, mechanical loading) on bone can enhance bone mass.[21–24] In addition, Robling et al[25] showed the importance of recovery periods for restoring mechanosensitivity to bone cells and maximising the osteogenic effects of mechanical loading (ie, PA).

In humans, daily PA appears to play an important role in maximising bone mass during childhood and the early adult years,[26] and studies in healthy adolescents have confirmed the findings of animal studies. Indeed, a PA programme with high-impact weight-bearing is seen as more beneficial to bone mass than one with no weight-bearing, such as cycling or swimming.[27 28]

Observational studies have shown a positive association between the amount of daily PA and BMD in healthy children and adults.[29 30] Vicente-Rodriguez et al[29] observed a negative association in 277 adolescents between sedentary lifestyles and bone health. Healthy adolescents spending more than 3 hour per day in sedentary
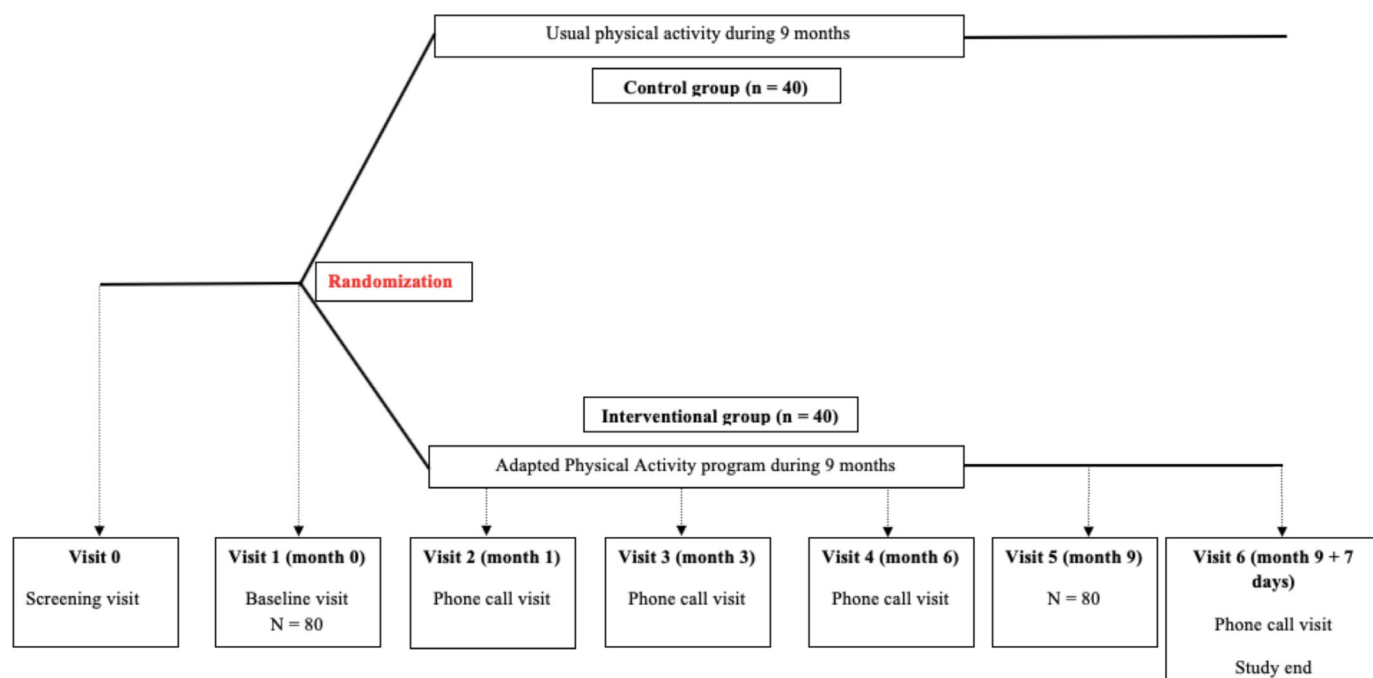
Figure 1 Design of the study.

behaviours (watching TV) had an increased risk of low bone mineral content. However, this association was modulated by participation in daily PA, suggesting that the negative consequences of excessive TV watching on adolescent bone health could be counteracted by sport participation.[29] Similarly, in healthy adults, Tonnesen et al[30] observed a positive association between duration of PA and BMD.

Only two studies have assessed bone health and PA in patients with IBD.[17 31] A randomised controlled trial investigated the effect of a PA programme on BMD in adult patients with CD.[31] Patients were randomised to a control group or a low-impact exercise programme of increasing intensity over a 12-month period. BMD increased significantly in the two groups with a 4.7% larger increase in the intervention group, independently of changes in potential confounding variables (eg, steroid dose, weight, diet).[31] Another study showed that daily PA, assessed objectively (ie, by accelerometry), was positively associated with BMD in paediatric patients with IBD.[17] This observational study highlighted the major role of daily PA in bone acquisition and development during growth. However, intervention studies investigating a causal relationship between a PA programme and BMD are needed to determine whether IBD paediatric patients could benefit from PA promotion programmes.

Primary and secondary objectives

The primary objective is to measure the effects of a 9-month high-impact exercise training programme (weight-loading activities) on whole-body BMD in paediatric patients with IBD. Secondary objectives are to evaluate whether the 9-month high-impact exercise training programme in paediatric patients with IBD improves BMD in the lumbar spine and trochanter, daily PA (time spent in MVPA), body composition (fat mass and fat-free mass), fatigue resistance, quality of life and inflammatory parameters.

METHODS AND ANALYSIS
Study design and procedures

This trial is a multicentre, randomised, controlled, blinded end-point study testing the efficacy of a high-impact exercise training programme during a consecutive 9-month period in paediatric patients with IBD (figure 1). From January 2020 onwards, consecutive paediatric patients with IBD followed in four Northern France hospitals will be asked to participate in this intervention study. The study will comprise six visits (table 1). At the baseline visit and the final visit, physical examination and measurement of BMD will be performed, and blood samples will be drawn. Patients will be asked to wear an accelerometer for 7 consecutive days and to complete a prospective dietary diary for 3 consecutive days at both the baseline visit and at visit 5 (V5; ie, the final visit at 9 months±1 day). At the end of the baseline visit, patients will be randomised at a 1:1 ratio to the intervention or control group. The randomisation sequence

Visit	Screening visit (V0)	Baseline (V1)	V2[†] (1 month±7 days)	V3[†] (3 months±7 days)	V4[†] (6 months±7 days)	V5 (9 months±15 days)	V6 (date of V5+7 days)
Information	X						
Written consent		X					
Inclusion and non-inclusion criteria		X					
Clinical assessment		X				X	
Vital signs		X				X	
Anthropometric measures		X				X	
Blood samples		X				X	
PCDAI/PUCAI*		X				X	
Bone age		X				X	
Bone mineral density		X				X	
Concomitant treatments		X				X	
Quality of life/fatigue score		X				X	
AE and SAE*			X	X	X	X	X
Randomisation		X					
Physical activity		X				X	
Dietary assessment		X				X	
Phone call			X	X	X		X

Table 1 Flow chart of the study

AE, adverse event; PCDAI, Pediatric Crohn's Disease Activity Index; PUCAI, Pediatric Ulcerative Colitis Disease Activity Index; SAE, serious adverse event.

will be provided by an independent statistician (who does not take part in assessing the patients at any point in the study) using computer-generated random numbers with block sizes of four. The block size information is not specified in the protocol to ensure that investigators will not be able to anticipate group assignment. The randomisation sequence is implemented in an electronic case report form (eCRF) system to ensure a centralised real-time randomisation procedure. Patients randomised to the control group will receive no instructions with respect to PA during the whole study period. Conversely, patients randomised to the intervention group will follow prospectively a high-impact exercise training programme with adapted physical exercises (weight-bearing activities) during the whole study period. For patients in the intervention group, three follow-up calls by telephone will be performed between baseline and the end of the study to assess the compliance of patients with the intervention programme and to note any adverse events (AEs) or serious AEs (SAEs). To control for unexpected events in either group (eg, hospitalisation, broken leg or other) that could impact adversely on exercise activities, we will record all AEs (minor or serious). Parents will be asked to report minor AEs and to call immediately in the case of SAEs. For patients included in the intervention group, visits V2, V3 and V4 will allow the collection of these data. For patients in the control group, data will be collected at V5 (interview with patient and parents) or by telephone in the case of SAEs.

Patient and public involvement

Patients in this trial will not be involved in the design, recruitment or conduction of the study. After the last visit, the patients will be informed by the study's physician of the results of bone health data in the form of pictures and text. The physician in charge of the patient will be also informed of the results to optimise treatment.

Participant eligibility

To be eligible for participation in the study, patients must meet the following criteria and not meet any exclusion criteria.

Inclusion criteria are (1) age between 6 and 18 years, (2) assent form signed by the patient and informed consent signed by parents (see online supplementary file), (3) diagnosis of IBD (CD, UC, IBD-U) for at least 6 months, (4) patient having a computer or smartphone with Internet access and (5) no simultaneous inclusion in other biomedical studies.

Exclusion criteria are (1) acute or chronic disease (other than IBD) associated with a decrease in PA, (2) any recent event (≤15 days) that could affect PA (eg, sprain, fracture, recent arthritis, anoperineal lesions, severe skin lesions), (3) no written assent from the patient and consent from parents (or legal guardian) and (5) positive blood pregnancy test at baseline visit.

Measurements

BMD and body composition will be measured by dual-energy X-ray absorptiometry and analysed blinded. Patients will be scanned in the supine position and the scans will be performed at high resolution. Because the BMD measurements are age-specific and sex-specific, standardised Z-scores will be calculated by subtracting the age-specific and sex-specific mean and dividing by the SD. In addition, bone age will be also used in order to adjust our calculation of BMD. According to WHO recommendations, BMD is considered abnormal with a T-score of ≥ −1 SD, osteopenia with a T-score of < −1 and > −2.5 SD, and osteoporosis with a T-score of ≤ −2.5 SD.[32]

Daily PA will be assessed by accelerometry. This method is an objective measure to assess PA in youth.[33] The triaxial accelerometer used will be the ActiGraph Monitor (model GT3X; ActiGraph, Pensacola, Florida, USA). It has been shown in children that accelerometer wrist placement promotes superior compliance compared with hip placement.[34] Therefore, patients will wear the accelerometer on the non-dominant wrist for 7 consecutive days in free-living conditions. Patients will be asked to follow their normal daily routine. After testing, the accelerometer will be removed and the data will be downloaded to a personal computer using the ActiLife software (V.6.13.4; Pensacola, Florida, USA). During the study, the accelerometer will be set to collect raw triaxial acceleration data at 60 Hz, stored in gravity (g) units ($1g$=9.81 m/s^2) with an epoch length of 1 s. Raw triaxial acceleration values are converted into one omnidirectional measure of body acceleration. For this, the vector magnitude will be taken from the three axes and then subtracted by the value of g as in $(x^2 + y^2 + z^2)^{1/2} − 1$, after which, negative values will be rounded up to 0, that is, Euclidean Norm Minus One.[35] Data will be analysed by the R-package GGIR facilitating data cleaning (non-wear detection) and data analysis (time spent in sedentary behaviours and MVPA).[35]

Quality of life and fatigue will be assessed respectively by the IMPACT-III questionnaire and the paediatric Functional Assessment of Chronic Illness Therapy-Fatigue (pedsFACIT-F) questionnaire.[36 37]

Energy intake will be assessed using a prospective dietary diary on 3 consecutive days including 1 weekend day. Patients will be interviewed on the type and amount of foods consumed over the three 24-hour periods. For greater accuracy, patients will be allowed to complete the dietary diary with their parents. Energy intake will be calculated with the KIDMENU software (SHS, Paris, France), using food composition tables from the French Food Safety Agency.[38]

Patients will have a detailed medical examination (weight, height, pubertal status and bone age using the Greulich and Pyle atlas).[39 40] In addition to serum 25(OH) vitamin D, haematocrit, C-reactive protein, albumin and erythrocyte sedimentation rate will be measured to assess inflammation and calculate disease activity. The Pediatric Crohn's Disease Activity Index (PCDAI) will be used for patients with CD and the Paediatric Ulcerative

Colitis Disease Activity Index (PUCAI) for patients with UC.[41 42] No score will be used for IBD-U.Finally, during medical examination, the physician will collect any events that could influence bone health (eg, disease duration, intensity of disease, corticosteroid lifetime, drug therapy during the study, fracture history, surgery) and PA (eg, practice at a club, type of practice, duration, frequency).

Intervention programme

The intervention programme consists of adapted physical exercises aimed at improving bone health. Since PA with weight-bearing is more beneficial to bone mass, the exercise programme will be to dynamically load the axial skeleton at the hip and lumbar spine sites using home-based, high-impact exercises. At baseline, patients randomised to the intervention group will receive a login and password to connect to the website (https://prophysicos.popsicube.fr/). Each exercise session will be downloadable on the website, and patients will click on the button 'start' to begin the session and on the button 'end' when exercises are completed. The duration of the session will be recorded and analysed to measure the compliance of the patient. For full compliance with the intervention programme, patients will have to perform exercises at least three times a week, with a minimum of 12 sessions per month; the duration of each session will be at least 15 min. Taking into account a review of controlled trials on intervention programme PA and bone health, we decided to plan a programme with 9 months of intervention.[43] As noted, PA as a weight-loading activity produces a force on bones that promotes bone growth and strength. As this force is commonly produced by impact with the ground, the type of exercises chosen for our intervention programme performed at home will consist of activities such as hopping, skipping, jumping, jumping rope and exercises with a step. Follow-up calls will be given at 1 (V2), 3 (V3) and 6 months (V4) to provide motivation and support to exercising individuals. The intensity of exercise will not be increased throughout the intervention programme. Indeed, the programme is intentionally easy to follow to allow individuals of different fitness levels and ages to achieve the benefits of the exercises.

Outcome measures

The primary efficacy outcome is the change from baseline to the end of the study (9 months) in whole-body BMD (in g/cm^2), assessed by dual-energy X-ray absorptiometry. Secondary efficacy outcomes are the changes from baseline to the end of the study (9 months) in:

▶ BMD assessed in the lumbar spine and trochanter (in g/cm^2) by dual-energy X-ray absorptiometry.
▶ Daily PA assessed by time spent in MVPA (average of 7 consecutive days, expressed in min/day) assessed by accelerometry.
▶ Body composition (fat mass and fat-free mass, expressed as % of body weight) assessed by dual-energy X-ray absorptiometry.

▶ Quality of life assessed by the total score of the IMPACT III questionnaire.
▶ Fatigue resistance assessed by the total score of the pedsFACIT-F questionnaire.
▶ Activity of IBD assessed by PCDAI (CD) or PUCAI (UC).

Safety outcomes

AEs are undesirable effects occurring during the trial. All AEs will be recorded on the medical file and reported in the eCRF, including the nature of each event, date of onset, duration, intensity, assessment of cause, causal relationship with the trial, action taken (eg, need for concomitant treatment) and outcome. According to the severity of AEs, the investigator will determine whether the participant should be withdrawn from the study and which follow-up procedures should be performed.

An SAE is defined as any untoward occurrence or effect that is life-threatening, requires prolonged hospitalisation, results in persistent significant disability, leads to a congenital anomaly or birth defect or causes death. In the case of SAEs, the investigator will report (within 24 hours) to the trial sponsor (Vigilance Unit of the Lille University Hospital Research Directorate) using the specific written form and record the SAE on the eCRF with signature and date.

Data collection

All data will be recorded by trained clinical investigators and/or the study co-ordinator using the eCRF developed with Clinsight (ENNOV) software (https://ecrf.chru-lille.fr/CSOnline/). Data safety and security measures are taken into account for the different study sites (restricted staff access, password protection, firewall and virus spyware protection). To ensure the data quality, a study monitor from the trial sponsor will verify and cross-check all data against the investigator's source document records. In addition, data will be monitored by the data management team of the Data Management Department of Lille University Hospital by using the predefined rules. In case of discrepancies, queries will be sent to the investigator and study co-ordinator for resolution. Data analysis will not be performed until the full database is closed.

Sample size calculation

Based on the literature, we expect a mean whole-body BMD value at inclusion of $0.645\pm0.1\,g/cm^2$ in our study population, and annual variation of 4.4% yielding to an expected mean value of $0.666\pm0.1\,g/cm^2$ at the end of the 9-month study in the control group (ie, a mean change from baseline of 0.021).[44] We assume that the mean whole-body BMD value after the 9-month PA training period will be higher than 10% of control group values, corresponding to a whole-body BMD value of $0.733\,g/cm^2$ (ie, a mean change from baseline of 0.088). To detect this effect size, with a two-sided test at the 0.05 level of significance, a power of 80%, an SD of 0.1 (assuming a correlation of 0.5 between baseline and 9-month follow-up values) with 36 subjects per group will be required. To account for an anticipated

rate of 10% of missing data (loss to follow-up), we plan to include a total of 80 subjects (40 per arm). As a conservative approach, the sample size calculation did not take into account the adjustment for baseline values.

Data analysis strategy

Statistical analyses will be independently performed by the Department of Biostatistics of Lille University Hospital and the Faculty of Medicine. Data will be analysed using SAS software version 9.4 (SAS Institute, Cary, North Carolina) and all statistical tests will be performed with a two-tailed alpha risk of 0.05. For data analysis, statisticians will be aware of the treatment group allocation. Baseline characteristics will be described for each treatment group; categorical variables will be expressed as frequencies and percentages and quantitative variables will be expressed as means±SD or medians (IQR) for non-Gaussian distribution. Normality of distributions will be assessed graphically and by using the Shapiro-Wilk test. No formal statistical comparisons of baseline characteristics will be performed; the clinical importance of any imbalance will be noted. All analyses will be performed using all randomised participants based on their original group of randomisation, according to the intention-to-treat (ITT) principle. The final report will be written based on the Consolidated Standards of Reporting Trials statement recommendations.

Primary outcome

The change in whole-body BMD from baseline to the end of the 9-month study will be estimated and compared between the two groups using the constrained longitudinal data analysis (cLDA) model proposed by Liang and Zeger.[45 46] This model will be used in view of the potential advantages of the cLDA compared with the conventional longitudinal analysis of covariance model. In the cLDA, both baseline and postbaseline values will be modelled as dependent variables using a linear mixed model (an unstructured covariance pattern model), and the true baseline means will be constrained to be the same for the two groups. The between-group mean differences in the 9-month change in whole-body BMD will be estimated by the time-by-arm interaction as treatment effect size. If the assumption of normality of model residuals is not satisfied (even after log-transformation), non-parametric analysis will be used; absolute changes between the baseline and 9 months will be calculated and compared between the two groups using non-parametric analysis of covariance adjusted for baseline values.[47 48] Under the ITT principle, all patients who are randomised are included in the primary efficacy analysis. In case of missing primary outcome measures (whatever the reason), missing values will be treated by a multiple imputation procedure. Missing data will be imputed under a missing-at-random assumption by using a regression switching approach (multivariate imputation by chained equations with m=10 imputations) with a predictive mean matching method for continuous variables and logistic regression models (binomial, ordinal or multinomial) for categorical variables.[49] The imputation procedure will be performed using the main baseline characteristics and allocated groups. Treatment effect estimates obtained in multiple imputed datasets will be combined using Rubin's rules.[50] A complete case analysis will be performed as sensitivity analysis.

Secondary outcomes

Secondary efficacy outcomes (9-month change in lumbar spine and trochanter BMD, time spent in MVPA, body composition, quality of life score, fatigue score and PCDAI/PUCAI score) will be analysed similarly to the primary outcome.

For AEs, only the rate of patients with at least one AE and SAE will be compared between the two groups (based on subject counts and not on event counts) using a χ^2 test or Fisher's exact test. The rate of specific AEs will be evaluated descriptively.

Ethics and dissemination

Before participating in the programme, the study aims and objectives will be carefully explained, and written informed assent will be obtained from each patient and consent for his/her parents or legal guardian by the physician. The study was approved by the Research Ethics Committee (Comité de Protection des Personnes, Sud-Ouest and Outre-Mer III, Bordeaux, France, No 2018/27) and the ANSM (Agence Nationale de Sécurité du Médicament et des Produits de Santé, Paris, France). All procedures will be performed according to the ethical standards of the Helsinki Declaration of 1975, as revised in 2008, and the European Union's Guidelines for Good Clinical Practice. According to the General Data Protection Regulation, data collection was approved by the National Commission on Informatics and Liberty (CNIL). At the end of this study, all documents (case report forms, patient source documents, and written informed consent forms) will be sealed and archived for 15 years at an archiving company (Iron Mountain, Wattrelos, France). In addition, all data from the e-CRF will be saved, burned on a DVD and archived for 15 years.

The outputs of this project will be disseminated in peer-reviewed journals and presented at scientific meetings on nutrition, sport sciences, gastroenterology, paediatric gastroenterology and IBD. In addition to the scientific community, one of the key objectives is to make the results available for patients and patient organisations (Association François Aupetit: https://www.afa.asso.fr/). This dissemination will be performed in writing and orally (eg, through letters, posters, conferences).

Author affiliations

[1] Univ. Lille, Inserm, CHU Lille, U1286 - INFINITE - Institute for Translational Research in Inflammation, F-59000 Lille, France, Lille, France
[2] Division of Gastroenterology, Hepatology and Nutrition, Department of Paediatrics, Lille University, Jeanne de Flandre Children's Hospital, Lille, France
[3] Univ. Lille, CHU Lille, ULR 2694 – METRICS: Evaluation des technologies de santé et des pratiques médicales, F-59000 Lille, France, Lille, France
[4] Department of Paediatrics, Caen University Hospital F 14000 Caen, France and Normandy University, Caen, France

⁵Pediatric Unit, Le Havre Hospital, Le Havre, France
⁶Department of Paediatrics, Amiens University Hospital and University of Amiens, Amiens, France

ORCID iD
Jérémy Vanhelst http://orcid.org/0000-0002-0570-1522

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