RESEARCH PROJECT

NÚCLEO DE GASTRENTEROLOGIA DOS HOSPITAIS DISTRITAIS 2020

TITLE: ***The role of Intestinal Ultrasound for early screening of inflammatory bowel disease in patients with HLA-B27 spondyloarthropathies and/or uveitis"***

A. STUDY INVESTIGATORS

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B. RESEARCH PROPOSAL

1. SCIENTIFIC AIM

Inflammatory bowel disease (IBD) is an emerging global disease, with an increasing incidence all over the world[1], which can lead to irreversible bowel damage and reduced quality of life. An early diagnosis of IBD is crucial to prevent bowel damage progression. Currently, ileocolonoscopy is the gold standard for screening for IBD[2]. Nonetheless, due to the invasiveness and potential complications of endoscopy, non-invasive imaging methods for screening of IBD are emerging. Intestinal ultrasound (IUS) is a non-invasive, wide available and low-cost method, which allows the evaluation of both large and small bowel inflammation and it is increasingly being performed by gastroenterologists themselves in IBD.

Several populations, such as patients with other auto-immune diseases, are at an increased risk for developing IBD. In these patients, an early screening for bowel disease would provide an opportunity to a timely diagnosis of IBD and implement early treatment. Patients with HLA-B27 spondyloarthropathies (SpA) and/or uveitis have an excess risk of IBD[3] and to date there are no specific recommendations on how and when to screen for bowel inflammation in this population. Our **global aim** is to evaluate IUS accuracy as an early screening method for inflammatory bowel disease in patients with HLA-B27 spondyloarthropathies and/or uveitis.

Primary objective:

- To analyse and compare the findings on IUS and ileocolonoscopy (IC) in patients with HLA-B27 SpA and/or uveitis.

Secondary objectives:

- To compare intestinal inflammation on IUS with faecal calprotectin levels;
- To compare intestinal inflammation on IUS with intestinal histology obtained during ileocolonoscopy;
- To compare intestinal inflammation on IUS with disease severity (BASDAI score for SpA and SUN for uveitis).

2. BACKGROUND

HLA-B27 prevalence varies by geographic region with an estimated prevalence in the Western European population of 4-13%[4]. The presence of HLA-B27 allele strongly contributes to a greater susceptibility for developing SpA, acute anterior uveitis (AAU) and, less frequently, inflammatory bowel diseases[5]. Acute anterior uveitis is the most common form of uveitis and HLA-B27 associated uveitis accounts for 18-32% of anterior uveitis in western countries[6]. Uveitis is often associated with seronegative SpA, occurring in approximately 20% to 40% of patients.

There is a very close link between IBD and SpA or uveitis. The phenotype of uveitis associated with IBD is often bilateral and occurs less often than in other SpA (2-9%)[7]. Several studies show the presence of subclinical gut inflammation in up to two-thirds of patients with SpA, shown either by endoscopy, histology or augmented faecal calprotectin[3]. In these patients, around 5-20% will develop CD within 5 years[8]. Development of IBD is associated with disease activity, spinal pain scores at baseline and worse physical function[8].

Being a population at increased risk of IBD, the early screening for intestinal inflammation is crucial in patients with HLA-B27 SpA and/or uveitis. Ileocolonoscopy is the gold-standard for the diagnosis of IBD, however it is an invasive method prone to potential complications[2]. Meta-analyses and recent guidelines have shown that IUS, Computed Tomography and Magnetic Resonance Enterography (MRE) have comparable diagnostic accuracy for the initial assessment of IBD[9, 10]. The advantages of IUS over other imaging modalities are its wide availability and low cost[11].

In addition to imaging methods, biochemical assessment is also an important component for screening for IBD. Faecal calprotectin seems to be the most sensitive marker of intestinal inflammation in this disease, demonstrating a good correlation with endoscopic indices of disease activity[12].

Significance and innovation

This is an innovative project that will enable the creation of a common protocol for early screening of IBD in patients with HLA-B27 SpA and/or uveitis. These results will be obtained in a real-life context, and so could be generalized for our current clinical practice. Thus, our study will contribute to better characterize gastrointestinal manifestations in our study population, enabling an earlier IBD diagnosis and consequently capacitating physicians to perform a timely therapeutic plan.

3. METHODS

3.1. STUDY DESIGN AND PROCEDURES

We propose to conduct a prospective study, taking place at Beatriz Ângelo Hospital, in patients diagnosed with HLA-B27 SpA and/or uveitis (according to ASAS criteria and ophthalmologic observation) with or without gastrointestinal (GI) symptoms. All participants will be submitted to an initial assessment through a questionnaire intended to evaluate baseline characteristics of the disease and the presence of GI symptoms (Appendix 1). Severity scores include Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) that consists of a one through 10 scale used to answer questions related to the major symptoms of AS (Appendix 2) and a grading of ocular inflammation in uveitis proposed by the Standardization of Uveitis Nomenclature (SUN) group (Appendix 3) will be used.

The study will include two phases (Appendix 4). Participants will be divided according to the presence or absence of GI symptoms, and on a first timing, only participants with GI symptoms will be assessed. Initially, an evaluation with blood samples (for haemoglobin, platelets and C-reactive protein), faecal calprotectin and IUS will be performed. Faecal calprotectin will be considered positive if > 150 ug/g[13]. All these patients will then be submitted to an ileocolonoscopy and results will be compared.

US examination without fasting will include evaluation of all large bowel segments (excluding rectum) and the small bowel. Bowel wall thickness (BWT) will be measured both in transverse and longitudinal sections. We define an increased BWT as >3 mm for all segments[11, 14]. The average value of two measurements in cross-section and two measurements in longitudinal of the affected intestinal segment will be considered. Loss of bowel wall stratification will be documented, as well as other complications (strictures, fistulae/abscesses, mesenteric

hypertrophy, lymphadenopathy, and ascites). The vascularity within the bowel wall will be assessed by Doppler examination using the Limberg score[15]. US examinations will be performed by an experienced gastroenterologist using an US device with convex (3–6 MHz) and linear (7–12 MHz) probes.

Ileocolonoscopy will be performed after a standard bowel cleansing with polyethilenoglicol. The ileocolonoscopy will be performed by an experienced endoscopist who will not be aware of the IUS findings. If IBD is suspected, endoscopic activity will be measured using the Simple Endoscopic Score for Crohn's Disease for CD and Mayo endoscopic subscore for ulcerative colitis[16]. Even in the absence of macroscopic disease, two biopsies from each segment (ileum, right and left colon) will be collected to assess for histological inflammation.

If similar results are found between IUS and ileocolonoscopy, on a second timepoint, participants with no GI symptoms at baseline will be submitted to IUS and faecal calprotectin. If there is evidence of intestinal inflammation on IUS or elevated faecal calprotectin, patients will be submitted to an ileocolonoscopy (Appendix 4). In patients with suspected small bowel disease, an MRE will also be performed as standard of care.

3.2. STUDY POPULATION

Inclusion Criteria

- Age > 18 years;
- HLA-B27 positive SpA and/or HLA-B27 positive uveitis;
- No previous diagnosis of inflammatory bowel disease.

Exclusion Criteria

- Pregnancy;
- Post-bowel resection surgery (terminal ileum or colon) or ileal stoma.

3.3. STATISTICAL ANALYSIS AND FEASIBILITY

Sample size

Assuming an anticipated prevalence rate of clinical and subclinical IBD in patients with HLA-B27 SpA and/or uveitis of 25%, a minimum acceptable percent agreement between two modalities (IUS and IC) of 70% and an expected percent agreement in the study of 85%, we would need 55 patients, under the significance level of 0.05 and power of 0.80. Sample size was calculated using the nomogram described by Hong *et al.*[17]. Assuming a 10% loss to follow-up and dropout rate, we will need to include a total of 61 patients.

Feasibility

Our centre is a multidisciplinary auto-immune disease centre, which follows around 1500 patients with auto-immune diseases. We have 8 dedicated physicians from Internal Medicine, Ophthalmology and Gastroenterology, and 7 fellows in training. The gastroenterology department at our hospital has experience in performing IUS in IBD patients and one of the nuclear investigators has specialized training in IUS (>300 exams).

We expect to enrol a total of 61 patients with HLA-B27 SpA and/or uveitis. Based on our centre registry we follow around 100 patients with HLA-B27 positive spondyloarthropathy and/or

uveitis. Therefore, it is feasible to include a total of 61 patients, recruited over a 1-year period. If we experience a slower recruitment than expected, we will consider including other centres.

Statistical analysis

Statistical analysis will be performed in order to compare IUS findings with findings on ileocolonoscopy. Basic descriptive statistics will be used, and continuous variables will be described as mean, median and range, while categorical variables will be expressed as frequency and percentage. The correlation between the IUS and IC variables used to estimate intestinal inflammation will be analysed using the Kappa (κ) index. The ability of IUS predicting intestinal inflammation will be determined by calculating its sensitivity, specificity, positive and negative predictive values and odds ratio.

A ROC curve analysis will also be performed and the area under the curve for IUS and ileocolonoscopy prediction of intestinal inflammation will be calculated and compared. The accuracy of faecal calprotectin prediction of inflammation will also be calculated.

The BASDAI and the faecal calprotectin levels of both group of patients (with and without inflammation on IUS) will be calculated and compared through a Wilcoxon-test or a t-test, according to the variable's adjustment to a normal distribution.

A p-value <0.05 will be considered statistically significant. Statistical analysis will be performed using Stata package version 16 and Statistical Package for the Social Sciences (SPSS, IBM).

3.4. STUDY TIMELINE

The study protocol has already been submitted for consideration and approval to the research ethics committee. The study follows the Declaration of Helsinki. A given informed consent from all participants will be obtained.

The study will start in October 2020.

- Data collection (recruitment of patients, collection of clinical, laboratory, US and IC data and record it on eCRF): 1 year
- Data and statistical analysis: 2 months
- Data presentation: 2 months
- Manuscript preparation and revise: 2 months

4. BUDGET

Description	Costs
Development and monitoring of eCase report Forms	€2.600
Study co-ordinator (12-month period)	€5.000
Intestinal ultrasound (61 patients)	€2.000
Faecal calprotectin measurement (61 patients)	€3.500
Statistical analysis	€3.600
Indirect costs (20%)	€3.340
TOTAL	€20.040

Given the budget, this project has also been submitted to the European Crohn's and Colitis Organisation (ECCO) – International Bowel Ultrasound Group (IBUS) grant.

5. REFERENCES

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APPENDIX 1

Questionnaire

General Information

Patient number: _____

Date of birth: ___/___/_____ Gender: Male ___ Female ___

Date of questionnaire: __ / __ / ___ In presence___ By phone___

Medical History

HLA-B27 syndrome: Spondyloarthropathy ___ Uveitis ___

Age of disease onset: _____ *years*

Clinical manifestations:

Back pain ___ Peripheral arthritis ___ Enthesitis ___

Ocular pain ___ Eye redness ___ Blurred/decreased vision ___

Disease activity BASDAI _____ ASAS _____ (inactive ____ low activity ___ high activity ____ very high activity ____) SUN (last evaluation) Cells_____/Flare ____

Uveitis: Acute __ Recurrent __ (<3 episodes/year ___ >3 episodes/year___) Chronic __

Vitritis __ Episcleritis/scleritis ___ Other ocular diagnosis _____

Therapeutic in use: Topical therapy ___ Intravitreal ___ Systemic corticosteroids ___ Immunosuppressive conventional ___ Biologic therapy ___

Family history of inflammatory bowel disease: Yes ___ No ___

Smoker: Yes ___ No ___

Frequent use of non-steroidal inflammatory drugs: Yes ___ No ___

Personal history of tuberculosis: Yes ___ No ___

Clinical symptoms at recruitment date

Constitutional symptoms: Fever ___ Weight loss ___ Others___

Gastrointestinal manifestations: Yes ___ No ___ If Yes, for how long: _____ m*onths*

If present, what are the symptoms: Nausea/Vomiting ___ Dyspepsia ___ Dysphagia ___ Constipation ___ Diarrhoea ___ (If diarrhoea present, number of liquid stools per week ___) Abdominal distention ___ Faecal urgency ___ Blood in stools ___

Abdominal pain ___ Perianal Lesion ___ Abdominal palpable mass ___

APPENDIX 2

The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

Please place a mark on each line below to indicate your answer to each question relating to the past week

1. How would you describe the overall level of fatigue/tiredness you have experienced?

NONE _____ VERY SEVERE

0 1 2 3 4 5 6 7 8 9 10

2. How would you describe the overall level of AS neck, back or hip pain you have had?

NONE _____ VERY SEVERE

0 1 2 3 4 5 6 7 8 9 10

3. How would you describe the overall level of pain/swelling in joints other than neck, back, hips you have had?

NONE _____ VERY SEVERE

0 1 2 3 4 5 6 7 8 9 10

4. How would you describe the overall level of discomfort you have had from any areas tender to touch or pressure?

NONE _____ VERY SEVERE

0 1 2 3 4 5 6 7 8 9 10

5. How would you describe the overall level of morning stiffness you have had from the time you wake up?

NONE _____ VERY SEVERE

0 1 2 3 4 5 6 7 8 9 10

6. How long does your morning stiffness last from the time you wake up?

_____

0 hrs 1 2 or more hours

0 1 2 3 4 5 6 7 8 9 10

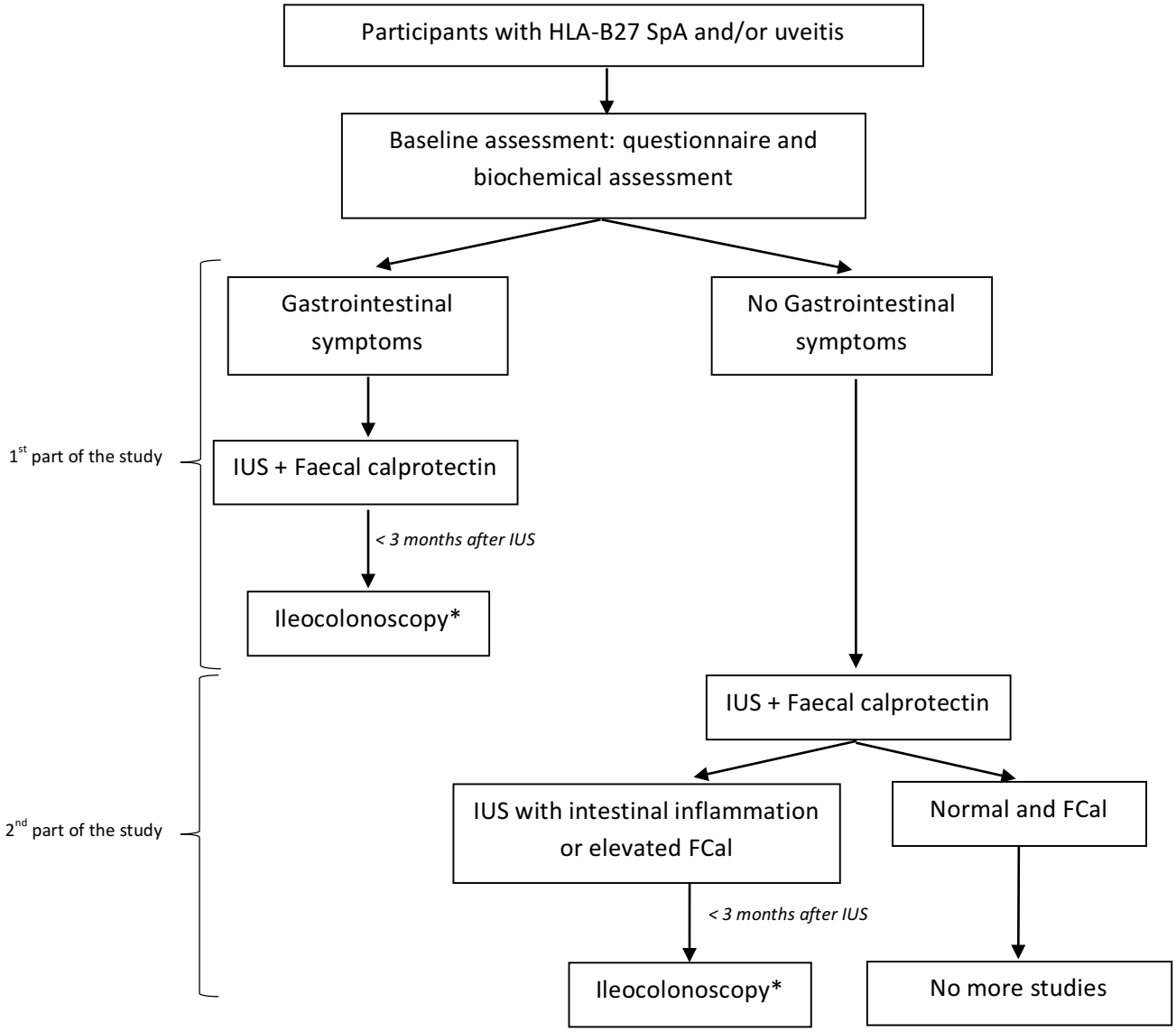
APPENDIX 3

The SUN Working Group Grading Scheme for Anterior Chamber Cells	
Grade	Cells in field
0	<1
0,5+	1-5
1+	6-15
2+	16-25
3+	26-50
4+	>50

The SUN Working Group Grading Scheme for Anterior Chamber Flare	
Grade	Description
0	None
1+	Faint
2+	Moderate (iris and lens details clear)
3+	Marked (iris and lens details hazy)
4+	Intense (fibrin or plastic aqueous)

APPENDIX 4

Study flowchart:



** Plus MR enterography in selected patients*

FCal – faecal calprotectin; IUS – intestinal ultrasound.