FACULTY OF MEDICINE

Efficacy of methotrexate to prevent postoperative recurrence of Crohn's disease

FINAL DEGREE PROJECT

Author: Mònica Munera Campos

Tutor: David Busquets Casals

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1. ABSTRACT

BACKGROUND: endoscopic postoperative recurrence (POR) of Crohn's disease (CD) is the presence of lesions in previously unaffected intestinal segments and occurs in up to 85% of patients one year after bowel resection. Patients at low risk for POR can either remain untreated until lesions recur or receive immediate prevention after surgery with mesalazine, azathioprine (AZA) and/or metronidazole, although with moderate benefit. Out of the postoperative setting, methotrexate (MTX) has been shown to be efficacious for induction and maintenance of remission and has been established as the second-line immunosuppressant for patients with CD unresponsive or intolerant to AZA.

AIMS: to determine the efficacy and safety of MTX to prevent endoscopic and clinical POR at 24 weeks after surgery in low risk patients.

METHODS: the study consists on a multicenter, randomized, double-blind and placebo-controlled clinical trial that will enroll 132 patients at low risk for POR (non-smokers, first intestinal resection, non-penetrating behavior). Patients will be randomized to receive subcutaneous MTX at doses of 25 mg/week or an identical placebo, for 24 weeks. Endoscopic and clinical assessment of POR will be performed after 24 weeks (6 months) of treatment. The main outcome is endoscopic POR, defined as a Rutgeerts score of $\geq$i2, and secondary outcomes include clinical POR, defined as $\geq$i2 lesions plus a Crohn's Disease Activity Index (CDAI) $\geq$150, and description of adverse events.

KEYWORDS: Crohn's disease; postoperative recurrence; methotrexate.

2. ABBREVIATIONS

A	Age at diagnosis (Montreal classification)
ADA	Adalimumab
AEMPS	Agencia Española de Medicamentos y Productos Sanitarios
AIEC	Adherent-invasive *Escherichia coli*
Anti-TNF	Anti-tumor necrosis factor
ARR	Absolute Risk Reduction
AZA	Azathioprine
B	Behavior of Crohn's disease (Montreal classification)
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CEIC	Comitè ètic d'investigació clínica
CI	Confidence interval
CRP	C-reactive protein
CS	Corticosteroids
EIMs	Extraintestinal manifestations
GI	Gastrointestinal
IBD	Inflammatory bowel disease
IFX	Infliximab
IM	Intramuscular
ITT	Intention-to-treat
IV	Intravenous
L	Location of Crohn's disease (Montreal classification)
MP	Mercaptopurine
MRI	Magnetic resonance imaging
MTX	Methotrexate
NNT	Number needed to treat
p	Perianal disease (Montreal classification)
POR	Postoperative recurrence
RR	Relative Risk
SC	Subcutaneous
UC	Ulcerative colitis

3. CLINICAL INTRODUCTION

3.1. GENERAL VIEW OF CROHN'S DISEASE

3.1.1. Concept

Crohn's disease (CD), as ulcerative colitis (UC), is an inflammatory bowel disease (IBD), a term that defines a chronic gastrointestinal (GI) inflammation. This chronicity consists on the alternation of remission with clinical relapses.[1]

UC consists on colon inflammation usually involving the rectum. It extends proximally in a continuous spread and is limited to the mucosa. In contrast, CD is transmural and can involve any area of the GI tract, as a segmental process leaving some areas unaffected.[2] Both CD and UC can develop extraintestinal manifestations (EIMs) as erythema nodosum, ankylosing spondylitis and primary sclerosing cholangitis.[1]

3.1.2. Epidemiology

The highest incidence of IBD is seen in Western countries, suggesting that lifestyle could be a risk factor. In the last decades, incidence in North America and Europe has reached a plateau, while previously considered areas with lower incidence rates have experienced a rise in new cases, pointing at a global health problem.[2]

Spanish incidence rates (cases per 100.000 per year) vary from 5 to 18 for UC and 3.9 to 7 for CD and the prevalence of IBD is estimated in a 1%. IBD has a bimodal distribution with a first peak of onset at 20-30 years and a second one, although lower, at elderly. CD appears 5 to 10 years earlier than UC. Males and females have similar incidence rates.[2]

3.1.3. Etiology and risk factors

Although it remains unknown, the general consensus is that in a genetically predisposed individual the intestinal microbiome, immune responses and environment trigger IBD.[3]

IBD is a polygenic disorder with 163 associated loci.[3] A first degree relative has a lifetime risk of 10% for IBD and the influence of genetic factors is greater in CD than UC.[2] Those

genes may play a role in the control of intestinal immunity. For instance, NOD2/CARD15 mutations occur in a 50% of CD patients[2] and result in dysfunctional immune responses leading to chronic inflammation.[2,3] Patients with CD show also dysfunctional autophagy, defective epithelium, decreased antibacterial agents and invasion by microbes, as adherent invasive *Escherichia coli* (AIEC).[3]

As an external and modifiable factor, active smoking, while protective for UC, confers a twofold increased risk of CD and a worse prognosis in these patients.[2,3] Other proposed factors include low vitamin D levels, nonsteroidal anti-inflammatory drugs and anxiety.[3]

3.1.4. Main features of Crohn's disease

Most patients (40-55%) have ileocolonic disease in the terminal ileum and cecum. Lesions affecting upper small bowel or other GI locations are rare. In contrast to UC, rectum is often spared.[1,2] Histologically, the non-caseating granuloma is a specific feature in CD and other lesions include crypt distortion, focal crypt abscesses and aphthous ulcers.[1]

Because of its heterogeneity, Montreal classification (ANNEX 1) is used to define subgroups of CD according to: age at diagnosis (A), location (L) and behavior (B) of disease.[2]

- Early onset of CD (A1) is associated with more extensive lesions and may involve the upper GI tract, while colon is more affected in older patients (A3).[2]
- Ileal location (L1) occurs in 30% of cases and consists on distal ileum disease with or without cecal involvement. Stenosis at those levels cause nausea, vomiting and right iliac fossa pain. In contrast, colonic location (L2), present in 20% of cases, involves any part of the colon and thus, it is characterized by severe diarrhea and rectal bleeding. As mentioned, ileocolonic location (L3) is the most frequent one and is defined by disease in the terminal ileum, with or without cecal involvement, in combination with colonic disease. Thus, it shows L1 and L2 manifestations. The upper GI location (L4), with a low frequency (5%), is considered when disease affects any GI location proximal to distal ileum. It can be in combination with L1-L3 and additional manifestations include dyspepsia, nausea, vomiting, epigastric pain and malabsorption.[2]

- Inflammatory pattern (B1) shows histological inflammation and ulcers leading to diarrhea and abdominal pain. Stricturing behavior (B2) consists on stenosis formation and obstructive or pseudo-obstructive manifestations, with abdominal pain and distension, nausea and vomiting. Penetrating disease (B3) tends to free perforation, abscesses and the presence of intern or extern fistulas, involving not only bowel but also skin, urinary bladder or vagina. Perianal disease (p) can be associated to any of these patterns. B2 and B3 have a higher need for surgery in the course of the disease.[2]

3.1.5. Diagnosis

Diagnosis of CD is based on the combination of clinical, radiological, endoscopic and histological features, recognized in Lennard-Jones criteria (ANNEX 2). Moreover, infections, ischemia, neoplasms and other inflammatory conditions as UC, need to be excluded.[4]

3.1.6. Medical management

As a chronic and heterogeneous process with no cure, treatment is always individualized. However, all smokers should be advised to quit as it is associated with a better response to treatment and an improved prognosis.[4]

Crohn's Disease Activity Index (CDAI) is used to assess the presence of disease activity and its severity (ANNEX 3). In general terms, relapses are managed with corticosteroids (CS). Some mild cases may be managed with budesonide, a CS of local action, but moderate relapses require systemic CS and severe ones should receive intravenous (IV) CS. This therapy should then be gradually stopped. A 30% of patients are refractory to CS and a proportion of responders may develop dependence and thus, once CS doses are decreased or stopped, relapse occurs. In these situations, induction of remission can be achieved by using immunosuppressants, anti-tumor necrosis factor (anti-TNF) agents or surgery.[4]

Once active disease has remitted, maintenance of remission can be achieved with thiopurines, both azathioprine (AZA) and mercaptopurine (MP), which are the first-line immunosuppressants while methotrexate (MTX) is considered as a second-line drug.

Relative new anti-TNF agents, infliximab (IFX) and adalimumab (ADA), are also considered in severe disease and their efficacy has supposed an impact in the management of CD.[4]

3.2. SURGERY IN CROHN'S DISEASE

3.2.1. Epidemiology

Surgery becomes necessary for most CD patients in the course of their disease. Nowadays, despite the use of powerful treatments, as immunosuppressants and anti-TNF agents, approximately a 50% of patients will need surgery within 10 years after diagnosis and lifetime risk is up to 80%.[5,6]

3.2.2. Indications and general procedures

Surgery is generally considered in patients with severe drug-refractory relapse, described as the persistence or worsening of symptoms despite the correct use of medical therapies, or when complications appear, such as bowel stenosis, perforations, abscesses, fistulas, toxic megacolon or cancer, that cannot be managed with medical treatment.[2]

Independently of the indication and the surgical procedure underwent, surgery is not curative in CD and thus, the resection aims at relieving symptoms while preserving the major bowel as possible, as patients may need further surgeries with the increased comorbidity and the potential development of short bowel syndrome. Nowadays, surgery tends to be more conservative and less invasive not only for those reasons but also because it has been shown that non benefit arises from more extensive resections or longer section margins and therefore, surgery should be guided macroscopically and not by histological disease evaluation.[2]

In general terms, bowel resection is the procedure of choice, especially if ileocecal disease is present. The resection is then followed by bowel anastomosis (ANNEX 4) although in patients with colitis or perianal disease with bad general conditions, an ostomy can be performed in order to decrease morbidity until the definitive surgery can be done. However, when possible, a single-time surgery should be performed.[2]

3.3. NATURAL HISTORY OF POSTOPERATIVE RECURRENCE

Resection of the affected bowel is not curative and the norm is that CD develops in other intestinal segments that were previously free of lesions, which is defined as postoperative recurrence (POR).[6] It can be considered as endoscopic, histologic, clinical, radiological or surgical (need for further resection) POR.[6,7]

In randomized controlled trials, clinical POR is found in a 25% and endoscopic POR in up to 85% of patients in placebo arms after 1 year of surgery.[6] Accordingly, most patients will develop endoscopic POR in the first year, even in the first 6 months, and this rate does not seem to increase much more in the following years. However, lesions tend to progress and become more severe with time.[7] POR detected at ileocolonoscopy precedes symptoms[7,8] and the severity of mucosal lesions is a powerful factor determining the clinical course and the requirement for reoperation in the postoperative scenario.[8]

It has been repeatedly shown that disease recurs most commonly at or above the anastomosis performed in surgery after an ileocolonic or ileocecal resection (ANNEX 4). The neoterminal ileum and anastomosis site are easily assessed by ileocolonoscopy. Initial lesions consist on aphthous ulcers that become larger, with even the presence of nodules or intestinal narrowing. These lesions are formed de novo and not developed from any inflammation left at surgery.[7,8]

Surgical models have shown that fecal stream plays an important role in the development of POR.[9] This is highlighted by the absence of POR seen in most patients undergoing a diverting ileostomy, which prevents the fecal stream as it is diverted to the stoma.[9,10] Moreover, in an ileocolonic surgery, the resection of ileocecal valve itself modifies the microbiome, as normally it prevents bacterial reflux into the ileum. This could explain the increased anaerobic colonization of the neoterminal ileum, especially by *Bacteroides*, AIEC and *Fusobacterium.* [9]

3.4. RISK FACTORS FOR POSTOPERATIVE RECURRENCE

Stratifying patients according to their low or high risk for POR would lead to a better management in this setting.[10] However, most factors have shown conflicting results leading to a lack of a validated risk-assessment index.[6,10] This may be explained by the fact that most studies addressing this issue are retrospective and differ on the way of assessing POR and in the time of follow up.[11]

3.4.1. Patient-related factors

Smoking is a strong and modifiable independent predictor for POR. Active smokers have approximately a twofold increased risk for endoscopic, clinical and surgical POR and the risk is higher in heavy smokers compared to the mild ones.[6] Ex-smokers and non-smokers have similar POR rates, showing that cessation of tobacco use decreases its risk.[10]

Gender and family history of IBD are not consistent risk factors for POR.[6,10]

3.4.2. Disease-related factors

Patients who suffer penetrating CD (B3) have a twofold increased risk for POR and the disease-free interval is significantly shorter.[6] However, B3 pattern may sometimes be only recognized at surgery and the risk for subclinical penetrating CD has not been evaluated.[10]

Prior bowel resection is a consistent predictor and those cases would benefit from a more intensive prophylaxis for POR.[5,6,10] Some clinicians argue that, instead of being a risk factor itself, the benefit may come from preventing further development of short bowel syndrome that could appear as a consequence of numerous resections.[11] The same could be understood when considering short duration of disease prior to surgery or early age at onset of CD, but these ones have not been shown in association with POR.[6,10,11]

The length of bowel resection depends on disease extent. However, their impact on POR and the length limit for risk are not well-established. Histologic features in the resection specimen, as the presence of granulomas and myenteric plexitis, have also been evaluated but the significance of these findings is not yet fully understood.[6,10]

Conflicting data exist for disease location, drug therapy prior to resection, perianal disease, genetic factors (NOD2/CARD15 mutations) and serology markers. Thus, according to our current knowledge they cannot be used as predictors for POR.[6,10]

3.4.3. Surgery-related factors

Taking in mind the predilection for the anastomosis and the role of the fecal stream in POR, some authors suggested that side-to-side anastomosis could lead to less POR rates when compared to end-to-side anastomosis (ANNEX 4), as it leads to a better luminal diameter and thus, less relative stenosis, fecal stasis and bacterial overgrowth. However, studies have shown no difference according to the anastomosis technique.[10]

The performance of laparoscopic instead of open surgery does not affect POR rates, although laparoscopy improves postoperative recovery and should be performed when feasible. Postoperative complications are not currently considered predictors for POR.[10]

In summary, only few risk factors are consistent in agreement with most studies and include: active smoking, prior intestinal resection and penetrating behavior.[5,6,10]

3.5. DIAGNOSIS AND MONITORING OF RECURRENCE

3.5.1. Ileocolonoscopy

Ileocolonoscopy remains the gold standard[5] as it is the most precise procedure to detect endoscopic lesions, which precede clinical recurrence.[8]

Rutgeerts endoscopic score (ANNEX 5) was developed in early 1990s based on the examination of the ileum proximal to the anastomosis.[8] The earliest lesion of POR is the aphthous ulcer. It was shown that patients with more severe lesions ($\geq$i2 scores) had a higher risk of clinical POR than those with no or low-grade inflammation (i0 or i1 scores, considered as no recurrence). Thus, Rutgeerts score was found to be predictive of consequent clinical prognosis.[8,12]

There is a universal use of Rutgeerts score, normally utilized to assess recurrence at 6 or 12 months as a primary endpoint in clinical trials evaluating therapies in the postoperative setting. However, the performance of an ileocolonoscopy at 6 months after resection could be better as severe lesions found at 1 year may have a worse response to medical therapies.[12]

3.5.2. Clinical assessment

Nowadays, CDAI remains the gold standard to measure activity of CD in clinical trials evaluating drugs for induction and maintenance of remission and frequently used as their primary outcome, considering relapse a score of ≥150. However, it is less widely accepted in trials evaluating therapies to prevent the disease in the postoperative scenario.[13]

Clinical markers of CD activity, including CDAI and acute phase reactants such as C-reactive protein (CRP), are inadequate used alone for the detection of POR.[10,13] Patients may experience abdominal pain, diarrhea, dysmotility and other signs and symptoms which may just be developed as a consequence of the surgery itself or complications in the postoperative period instead of suggesting symptomatic POR.[10]

The CDAI of patients with clinical POR is higher than in patients still in remission. The distribution of symptomatic scores has its best association with Rutgeerts score when compared with endoscopic lesions categorized dichotomously by <i2 and ≥i2. For the five endoscopic categories considered alone, minimal linear relationship has been shown.[13]

CDAI has a sensitivity of 0.70 and specificity of 0.81 in the POR scenario and it should not be used alone as an outcome in clinical trials as it could lead to misleading conclusions. Firstly, the CDAI sensitivity could be improved by its combination with levels of CRP. However, it remains to be determined its predictive value in POR. Secondly, the CDAI specificity can be improved from 0.81 to 0.96 by its combination with Rutgeerts score. Thus, considering symptomatic recurrence as the presence of endoscopic disease (≥i2) plus a CDAI of ≥150 seems the most appropriate for this purpose.[13]

3.5.3. Emerging methods

Ileocolonoscopy is an invasive procedure, can be uncomfortable for patients and accurate identification of disease in the ileum, which should be explored to approximately 30 centimeters from the anastomosis, may not be achieved in few cases.[8,14] For these reasons, new methods for diagnosis of POR are being proposed, such as wireless capsule endoscopy (WCE), magnetic resonance imaging (MRI) enteroclysis and fecal markers.[10]

A small study reported that neoterminal POR was detected by WCE in higher rates than by ileocolonoscopy and that it was less invasive, with no need for sedation and well tolerated by patients.[14] In contrast, another study found that WCE was inferior to detect neoterminal POR but superior to detect proximal small bowel lesions not seen by ileoscopy. However, because a WCE was not performed preoperatively, it could not be known if those lesions were or not present before surgery and their clinical relevance is also unknown.[15] Thus, WCE has not replaced conventional endoscopy, but as an emerging tool should be considered, if available, when ileoscopy cannot be performed.[5]

MRI enteroclysis is an emerging technique that shows sites of inflammation with high contrast of soft-tissue allowing visualization of luminal, mural and extramural abnormalities[16] and it is not limited by radiation exposure.[10] There is an adequate correlation of Rutgeerts score and MRI enteroclysis index. However, prospective studies are needed for its implementation as a good image is not always achieved because of surgical clips or bad intestinal distention.[16]

Elevated fecal levels of calprotectin and lactoferrin, which are proteins released in inflammation, have been shown to be predictive of clinical relapse in CD and they have been recently studied as non-invasive markers of biological POR.[10] They correlate with lesions seen at endoscopy after ileocolonic surgery, suggesting that both, but especially calprotectin, are useful to predict POR. Its use could decrease costs and utilization of invasive methods.[17] However, further studies are needed to reinforce their utility in this context.[10]

3.6. MANAGEMENT OF POSTOPERATIVE RECURRENCE

Most therapies used for CD in induction and maintenance of remission have also been studied as prophylaxis of POR and currently there is not an established consensus on when, how and how long to treat after bowel resection. However, there is no doubt that CD patients should also receive advice to stop smoking after surgery.[5]

3.6.1. Mesalazine

The use of mesalazine for the prevention of recurrence has been studied in several clinical trials. Although it is interesting because of its low cost and its safety profile, controversy exists about its use.[18] A meta-analysis performed in 2009 found that the relative risk (RR) of endoscopic POR was scarcely reduced by mesalazine (RR:0.93, 95% CI:0.76-1.13) with a number needed to treat (NNT) of 8 and that reduction of clinical POR showed a similar tendency with a RR of 0.76 (95% CI: 0.62-0.94) and a NNT of 12.[19] The evidence suggests a limited effect of mesalazine and that, when used, it should only be considered in "low risk" patients.[5,10]

3.6.2. Probiotics and antibiotics

The higher bacterial counts and increased anaerobes proportion found in patients with CD after surgery suggested that manipulation of the intestinal microbiome, either by probiotics or antibiotics, could prevent recurrence. When different probiotics were compared to placebo to prevent POR, no differences for endoscopic or clinical recurrence were found. However, metronidazole and ornidazole, two nitroimidazole antibiotics, were compared to placebo and they were found to be efficacious in reducing the risk of severe endoscopic POR at three months (RR 0.44, 95% CI O.26-0.74) and clinical POR at one year (0.23, 95% CI 0.09-0.57) both with a NNT of 4.[20] However, their long-term use is limited because of frequent adverse events, such as neuropathy and GI intolerance, that lead to withdrawal of treatment.[18,20]

3.6.3. Thiopurines

Doherty *et al*[19] reported that, compared to placebo, AZA reduced the risk of severe endoscopic POR at 12 months with a RR of 0.64 (95% CI 0.44 to 0.92) and a NNT of 4. There were no significant differences between mesalazine and AZA/MP in reducing the risk of recurrence in the long-term, although endoscopic POR at 12 months was significantly lower with AZA/MP. However, adverse events profile was better for mesalazine.

Thiopurines are recommended to reduce the risk of POR but their benefit is actually moderate and drug withdrawal is frequent. Nowadays, treatment with AZA/MP can be considered as the first line prophylaxis, especially in "high risk" patients.[5] Moreover, it seems adequate to use a combination of AZA with metronidazole for the first 3 months after surgery.[5,21]

3.6.4. Anti-TNF agents

Recently, anti-TNF agents, especially IFX, have been evaluated to prevent POR. The early data suggests a higher benefit of anti-TNF therapy compared to placebo and to other drugs.[18] In a small open-label pilot study comparing IFX versus AZA, IFX group had lower endoscopic POR rates (9% vs. 40%) after 12 months of therapy, although no significant differences were found in clinical POR.[22] Further studies are needed to establish the role of anti-TNF agents but they could be the best option in "high risk" patients. However, because of their high cost and the unknown long-term safety profile, a careful selection of patients is required for their use.[18]

4. JUSTIFICATION:

Methotrexate (MTX), one of the oldest cytotoxic agents, is a folic acid antagonist that impairs DNA and RNA synthesis. It was first used as a chemotherapeutic drug and it has then proven efficacy in inflammatory diseases [23,24] as rheumatoid arthritis or psoriasis.[24]

In the past 25 years efficacy of MTX in treating IBD has been shown in numerous studies.[25] Nowadays, it is still unlicensed for its use in IBD[24] and clinically used in same indications as thiopurines, as a second-line immunosuppressant.[5] Although widely used, about 1/3 of patients are refractory to thiopurines[25] and intolerable adverse events occur in up to 28% of cases.[26]

On the one hand, MTX has demonstrated efficacy for induction of remission in refractory CD. In 1989, a non-randomized open label pilot study was conducted with 14 patients and, despite its limitations, it suggested for the first time the value of MTX in inducing remission.[25] Most studies in this context are not comparable because of different dosage and route of administration, small number of patients and outcome definition. Safety and efficacy of MTX were better demonstrated in 1995, in a large randomized placebo-controlled clinical trial using intramuscular (IM) MTX at doses of 25mg/week. A 39.4% of patients in the MTX group achieved clinical remission compared with 19.1% in the placebo group. Prednisone doses required by patients were also lower in the MTX group, which also achieved a better mean score of CDAI.[27]

On the other hand, IM MTX at doses of 15mg/week is effective for maintenance of remission in CD. In one clinical trial, 65% of patients in the MTX group maintained remission compared to 39% of the placebo group, with a NNT of 4. Other performed studies failed to show a benefit of MTX given orally and at lower doses.[28]

Although MTX is similar to AZA in efficacy and tolerability[29] it remains underused because of physicians concerns about hepatotoxicity.[25] Most common adverse events consist on GI manifestations (nausea, vomiting or mouth sores) and asymptomatic elevated liver

enzymes; other less frequent include hair loss, malaise and myelosuppression.[23,24] Actual hepatotoxicity, assessed by histological study, is rare[23] and folic acid supplementation reduces liver-related adverse events of MTX, while its benefit in GI, mucosal, cutaneous or hematological side effects may be slighter.[30]

Route of administration remains on debate as landmark clinical trials studying the efficacy of MTX, either in induction or maintenance of remission, have used subcutaneous (SC) or IM doses.[25] In a recent study, the bioavailability of oral MTX at doses of 25mg once a week was found to be 0.86 (90% CI: 0.79-0.92) compared to the same SC dose, but it could not conclude bioequivalence. Moreover, surgery or inflammation affecting duodenum and jejunum could decrease the absorption of MTX.[31] Folic acid and MTX are partly absorbed by a common transporter in the proximal bowel, but there is no evidence that oral bioavailability is affected when they are simultaneously administered.[32] Nevertheless, the parenteral route should be preferred and transferring to oral therapy should be individualized.[5,32] SC injections, usually administered in clinical practice, have similar pharmacokinetics and a greater tolerability compared to IM ones.[25,32]

Currently, most authors suggest two main different approaches in the postoperative setting: immediate prophylaxis in all patients who undergo a surgery versus prophylaxis tailored to endoscopic lesions, this is, giving only treatment when mucosal lesions are macroscopically present and thus, prophylaxis is then more related to clinical POR and, when feasible, mucosal healing. However, no differences have been found between these therapeutic attitudes.[10] Moreover, there is not a well-established consensus about which should be the postoperative treatment according to the "low" or "high" risk of POR.[5]

Firstly, for "low risk" patients, some authors recommend 3 months of metronidazole. Afterwards, endoscopic surveillance is recommended and if POR is present therapy should then be switched to anti-TNF agents; if not, surveillance should be continued.[18] Some others suggest an immediate use of thiopurines, when tolerated, with or without metronidazole for the first 3 months. If endoscopic lesions progress or clinical POR occurs,

anti-TNF agents should then be used.[11] In contrast, a step management suggests that patients can be left with no medication or with mesalazine and then, if ileocolonoscopy at 6 months reveals significant POR patients should receive anti-TNF agents.[33]

Secondly, it is more clear that "high risk" patients should always receive prophylaxis after surgery and now authors recommend either thiopurines, associated or not with metronidazole for the first 3 months, or anti-TNF therapy.[11,18,33]

In summary, as POR is the norm[6], a treatment to prevent or at least delay Crohn's lesions seems desirable. As endoscopic POR precedes symptoms[7,8] it is as reasonable to start an immediate treatment to avoid POR, as to perform a tailored treatment if endoscopic lesions are found.[11,18,33] As mentioned, mesalazine has shown a limited effect and nitroimidazole antibiotics are intolerable in the long-term. Although thiopurines are recommended, not all patients will respond or tolerate them. Anti-TNF agents could be an option for patients at high risk of POR, but their cost and unknown long-term safety makes selection of patients necessary.[5,19,20] Out of the postoperative setting, MTX has been established as the second-line immunosuppressant for CD.[2] With all these considerations in mind, a first approximation is needed to assess the efficacy of MTX in this scenario as it could offer a new option in the prevention of POR.

5. HYPOTHESIS

5.1. PRIMARY HYPOTHESIS

Therapy with methotrexate is efficacious to prevent endoscopic postoperative recurrence of Crohn's disease.

5.2. SECONDARY HYPOTHESIS

Therapy with methotrexate is also efficacious to prevent clinical postoperative recurrence of Crohn's disease. Methotrexate has also an adequate safety profile.

6. OBJECTIVES

6.1. PRIMARY OBJECTIVE

The main aim of this study is to evaluate the efficacy of methotrexate after surgery to prevent postoperative recurrence of Crohn's disease assessed by ileocolonoscopy at 24 weeks.

6.2. SECONDARY OBJECTIVES

- To evaluate the efficacy of methotrexate after surgery to prevent postoperative recurrence of Crohn's disease assessed by clinical criteria at 24 weeks.
- To evaluate the incidence of adverse effects from therapy with methotrexate at 24 weeks.

7. METHODOLOGY

7.1. STUDY DESIGN

A multicenter, phase II, randomized, double-blind and placebo-controlled clinical trial will be performed.[34] It will consist on the first study that assesses the use of MTX as a prophylaxis for POR of CD.

7.2. SUBJECTS OF THE STUDY

The study population will be all patients diagnosed with CD who undergo a bowel resection in each center participating in the study, between January of 2015 to December of 2017, and who meet the criteria established in this section.

7.2.1. Eligibility of the participants

- **Inclusion criteria:**
  - Signed informed consent.
  - ≥18 years of age.
  - Man or woman with a negative pregnancy urine test.
  - Use of adequate contraceptive methods.
  - CD diagnosed by classic Lennard-Jones criteria. (ANNEX 2)
  - Bowel resection of all macroscopically affected lesions: ileal, colonic, ileocecal or ileocolic resection (L1-L3). (ANNEX 1)
  - Resection is followed by anastomosis of non-affected ileum to normal colon: ileocecal, ileocolic or ileorectal anastomosis.
  - Surgery has been performed in a maximum of 2 weeks (+/- 5 days) prior inclusion in the study.

- **Exclusion criteria:**
  - Antecedents of intolerance or adverse events with the use of MTX.
  - Current contraindication for MTX. (ANNEX 6)
  - High alcohol consumption (≥7 units per week).
  - Planned pregnancy (men and women) within the next 12 months.

- Presence of 1 or more of the following risk factors for POR: active smoker, prior intestinal resection and/or penetrating behavior (B3).
- Presence of EIMs, perianal disease or other conditions that indicate a need for other therapies directed to CD, for instance anti-TNF agents.
- Active infection at the moment of the study.
- Impossibility for SC administration of the therapy.
- Refusal for the performance of the ileocolonoscopy at 24 weeks.

7.2.2. Subjects withdrawal criteria

- **Patient decision:** the subject can withdraw his/her consent to participate in this study at any time and for any reason and no other new data will be added to the database. At patient request, all previously added data will be destroyed from the study database. Withdrawal of patients from this study will not suppose any prejudice to the treatment and control of their disease.

- **Investigator decision:** the investigator in each center participating in this study can consider the convenience of withdrawal of a patient in case of the development of complications different from POR, such as EIMs or perianal disease, or any other condition that could require a specific treatment which could affect the development of this study.

- **Protocol withdrawal criteria:**

  Patients will be withdrawn from this study because of:

  - Belatedly identified violation of the inclusion and/or exclusion criteria.
  - A failure to complete the protocol requirements.
  - Pregnancy during the study period.
  - Any severe adverse event, unacceptable health risk or consequence for the participant derived from this study.
  - Apparition of intolerable clinical symptoms that cannot be explained by the postoperative state or other conditions before the performance of an ileocolonoscopy at 24 weeks. Patients receiving placebo and patients that appear to be unresponsive to MTX will be withdrawn from the clinical trial and will receive another tailored treatment to manage their disease.

7.3. SAMPLING

7.3.1. Sample selection

A consecutive non-probability sampling will be carried out as patients with CD undergo a bowel resection. Patients will be approached when the surgery is being planned in order to assess with enough time their potential participation, according to the predefined eligibility criteria. Every patient will be given the information about the study and if he/she is interested in participating he/she will be contacted by the principal investigator of the center in order to obtain the informed consent.

7.3.2. Sample size

GRANMO application was used to determine the sample size of this clinical trial. Because of the lack of studies that assess the proportion of patients being at low or high risk for recurrence and the lack of an established index for its risk at the moment of this study, we took into consideration that the proportion of patients having an endoscopic POR without treatment in 6 months is 60% regarding to the fact that it occurs in much more than half of patients in 1 year and that it mostly appears in the first months.[21] While other studies could expect higher recurrence rates, we assume a lower incidence in the control arm because of the exclusion of three risk factors according to our current knowledge (active smoking, prior bowel resection and B3 behavior).

We assume an endoscopic recurrence rate in the MTX group of 35%, that could be similar to the expected one for treatment with AZA.[21] We expect MTX can be discontinued in a maximum of 10% of patients[23] in the 6 months of therapy and we assume a global drop-out rate of 15%.

Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a one-sided test, with a reason between samples equal 1 and an anticipated drop-out rate of 15%, we will need 66 subjects in the MTX group and 66 subjects in the placebo group to achieve a relative risk (RR) for endoscopic POR of 0.583 for MTX versus placebo.

7.4. INTERVENTIONS

7.4.1. Randomization

All patients will be randomized after surgical intervention, once they meet the established criteria and have given their informed consent, to start treatment with MTX or placebo within the first 2 weeks (+/-5 days) after surgery.

Random assignation will be realized using a centralized system by a computer program, with a method of sealed envelopes and managed by the Pharmacy Service of the sponsor center. Sealed envelopes will only be open in case of necessity with prior notification to the Sponsor. The program will generate treatment allocations in a 1:1 randomization scheme in blocks of 4 patients, that is, we will randomize 4 patients at a time ensuring that 2 patients will be allocated to the MTX group and 2 patients to the placebo group. With this method, there are six different ways in which 4 patients can be assigned equally to our MTX or placebo group. The process will be the same for the total sample.

7.4.2. Degree of blinding

This will be a double-blind clinical trial. All investigators and physicians monitoring patients, both by clinical examination and ileocolonoscopy, and patients receiving either placebo or MTX, will be unaware of the intervention that has been assigned. The physician that performs the ileocolonoscopy will be different from the one that has assessed the patient within all the visits along the study.

7.4.3. Description of interventions

A) Description of treatment:

Within the 2 weeks (+/-5 days) after patients have undergone a bowel resection, they will start, depending on randomized treatment allocation, one of the following treatments:

- **MTX group:**

- Patients will receive a SC dose of 25mg of MTX once a week. The administration will be the same day of the week for each patient in order to ensure adequate dosage. The treatment will be administered in a 1 pre-filled syringe of injectable solution for each dose that has a clear, yellow to brown, appearance (ANNEX 6).

- In order to prevent or decrease adverse effects related to MTX, an oral folic acid supplementation will be given as in the current clinical practice, at a single dose of 5mg per week, 24 hours after MTX administration. The treatment will be administered in one pill for each dose that has a rounded and light yellow appearance.

- **Placebo group:**

- Patients will receive a placebo formulation in identical amount, appearance and route of administration as MTX given in the study group. Placebo will be administered once a week, at the same day of the week for each patient.
- In order to ensure the blinding of this study an oral placebo, with the same appearance as folic acid supplementation given in the MTX group, will be given orally once a week, 24 hours after the administration of the SC placebo.

B) Instructions for administration:

Once each patient is included in this study, he/she will be visited by a nurse. Patients will be instructed to inject SC treatment (MTX or placebo) by themselves or by their family members. It will be specifically remembered that administration has to be only once a week and they will also be warned about reproductive toxicity and the need of an adequate contraceptive method.

The responsible nurse will remember the need of choosing the same day of the week for its administration and will explain sites were SC treatment can be injected (abdomen, thigh, arms). It will also be explained that it is adequate to alternate between the right and left sides every week and to choose different locations within the same area. They will also be explained the need for return of syringes and blisters packs to the Pharmacy Service.

Nurses will also explain the adequate administration of the oral treatment (folic acid or placebo in each case) in the 24 hours after the SC treatment.

C) Accounting and dispensation of medication:

Placebo will be prepared by the Pharmacy Service of the sponsor center and the Principal Investigator will guarantee that the Pharmacy Service of each participating hospital receives the deliveries of medication. Those deliveries will be adequately registered and stocked and will only be dispensed to patients according to the protocol and following the

dispensation system in each hospital. Medications that are not utilized will be returned to the sponsor center or, alternatively, eliminated.

Traceability of the administered therapy will be ensured by a systematic register performed by the Pharmacy Service of each center. The Pharmacy Service will have accounting and inventory registers to monitor reception, dispensation and elimination of the medications of the study. It is needed to register the following information: number of patient, kit number, date and hour of dispensation and initials of pharmacist. At the end of this study, the pharmacist will perform a final inventory of medication.

D) Re-count and compliance of medication:

Compliance will be evaluated by the investigator in each visit of each patient by the information provided by the patient itself. Registers of medication by the Pharmacy Service will also be collected in Case Report Form (ANNEX 8). A dispensation/return system will be used. Periodically, patients will be given the medication by the Pharmacy Service in visits 2 to 8, and they will return at the same time the last medication given (syringes and blisters packs) in the next visit, from visits 3 to 9. Adherence to treatment will be studied in order to ensure protocol compliance and we will consider that adherence was adequate when 80% of doses were administered.

E) Adverse events:

All adverse events that are considered in relation with the therapy will be registered. As detailed, patients will be withdrawn from this study if severe adverse effects or unacceptable risk for health occur.

Asymptomatic increase of liver enzymes and mild adverse effects that can be tolerated by the patient without implying any risk for his/her health (for instance, mild asthenia or headache) will not be considered a criterion for patient withdrawal.

F) Concomitant treatments:

Any other therapy directed to treat CD, as mesalazine, corticosteroids, anti-TNF agents, thiopurines or antibiotics as metronidazole, are not permitted during this study. The need of any of those medications will be considered a failure of the intervention in study.

7.5. VARIABLES AND RESPONSE EVALUATION

7.5.1. Independent variable

The independent variable of this study is the therapy administered in each group this is, being randomly allocated in:

- MTX group, or
- Placebo (control) group

7.5.2. Dependent variables

- Primary endpoint:

- Endoscopic recurrence, that will be defined by the presence of macroscopic lesions shown by ileocolonoscopy performed to 30 centimeters from the neoterminal ileum at 24 weeks after treatment. Each physician that performs the ileocolonoscopy will collect 3 images that will be reviewed by the reference center, the sponsor center, in order to diminish interobserver variability in their assessment.
- Endoscopic lesions defined as POR will be those ones being classified as ≥i2 according to Rutgeerts endoscopic score (ANNEX 5).

- Secondary endpoints:

- Clinical recurrence: clinical POR will be evaluated at 24 weeks after the performance of ileocolonoscopy, and it will be defined by the presence of ≥i2 lesions (endoscopic POR) plus a CDAI score ≥150 (ANNEX 3).

- Adverse events: the apparition of adverse events related to therapy will be registered and treated in terms of incidence in each group.

7.5.3. Potential covariates

- Patient-related covariates:
  - Sex; male/female
  - Age; measured in years
  - Age at onset of Crohn's disease; measured in years
  - Age at resection; measured in years

- Family antecedents (yes/no)
- Weight; measured in kilograms

- Disease-related covariates:
  - Location of Crohn's disease (L1/L2/L3) (ANNEX 1)
  - Pattern of disease (B1/B2) (ANNEX 1)
  - Prior use of antibiotics (yes/no)
  - Prior use of mesalazine (yes/no)
  - Prior use of thiopurines (yes/no)
  - Prior use of MTX (yes/no)
  - Prior use of anti-TNF agents (yes/no)

- Surgery-related covariates:
  - Length of resected segment; measured in centimeters
  - Type of anastomosis (side-to-side/end-to-end/side-to-end) (ANNEX 4)
  - Postoperative complications (yes/no)
  - Granuloma at resection specimen (yes/no)
  - Myenteric plexitis at resection specimen (yes/no)
  - Disease present at resection margins (yes/no)

7.6. DATA COLLECTION AND VISITS CHRONOGRAM

Potential participants will be approached when the surgery is being planned. Demographic and clinical data will be obtained in that first visit, as well as the adequate evaluation of inclusion and exclusion criteria.

Visits and data that will be included in the study database at each time are specified in the Visits Chronogram (ANNEX 7) that will be applied to each participant. Each investigator is responsible for ensuring that all data is complete and exact, in an accurate and timely manner, and collected in Case Report Form (ANNEX 8) that will be electronically centralized and available for the Principal Investigator and for the Monitor.

A scheme of this clinical trial is presented in ANNEX 9.

8. STATISTICAL ANALYSIS

All the subjects that are randomized and start treatment will be included in the intention-to-treat (ITT) analysis and patients with a treatment adherence lower than 80% and those not reaching the endoscopic assessment at 24 weeks will be regarded as failures, and then will not be included in the per protocol analysis.

8.1. DESCRIPTIVE – UNIVARIATE ANALYSIS

- **Trial endpoints**

Endoscopic POR will be statistically treated as a binary categorical variable (recurrence: $\geq$i2; no recurrence: <i2). Clinical POR will be considered as a binary categorical variable defined by the presence of $\geq$i2 lesions plus a CDAI score $\geq$150. Adverse events will be described as frequencies in each group.

- **Potential covariates**

For the potential covariates, categorical variables will be expressed as relative frequencies. Continuous variables will be treated by mean ($\pm$ standard deviation) when normal distribution can be assumed; if not, median (interquartile range) will be used.

8.2. BIVARIATE ANALYSIS

- **Base-line characteristics and potential covariates**

Because of randomization, it is not expected to find differences in the distribution of potential covariates between MTX and placebo groups. However, a table with base-line characteristics will be performed in order to ensure those variables are equally distributed in both groups. (ANNEX 10; Table 1)

The same bivariate analysis will be performed for each potential covariate and the presence or absence of POR. (ANNEX 10; Table 2)

In both analysis, X^2 test will be used for categorical variables and t-Student for quantitative variables (or the correspondent non-parametric U of Mann-Whitney).

- **Effect of the intervention**

In the bivariate analysis for study outcomes, relative frequencies of endoscopic (primary endpoint) and clinical (secondary endpoint) POR at 24 weeks will be compared between MTX and placebo by using X^2 test. Adverse events (secondary endpoint) will only be described as frequencies in each group. (ANNEX 10; Tables 3, 4 and 5)

The magnitude of the effect of MTX will also be expressed as RR, absolute risk reduction (ARR) and NNT.

8.3. MULTIVARIATE ANALYSIS

For all those potential confounding factors (covariates) that have been studied in the previous analysis that show significant statistical difference, the treatment effect on recurrence will be adjusted by Poisson regression analysis.

Statistical analysis will be performed using *Statistical Package for Social Sciences* (SPSS) for *Windows®*.

Statistical differences will be considered with $p<0,05$.

This statistical analysis will be performed in two data analysis monitoring and in the final analysis at the end of the study.

9. LIMITATIONS OF THE STUDY

- The needed sample in order to obtain an adequate statistical difference is quite large, which will be solved by the collaboration of 12 hospitals, as a multicenter clinical trial.

- This clinical trial is designed with the aim at achieving a first approximation on the efficacy of MTX to prevent POR. However, it will not respond to other questions as how long should the treatment be continued or if the efficacy of MTX could be maintained when a switch to oral route of administration or a dosage decrease are required.

- This study is performed in a clinical scenario where there are many issues that remain to be determined. We have considered as "low-risk" patients for POR those ones lacking of a risk factor according to the current knowledge. However, a risk-assessment index is still lacking in this context and thus, we may be misclassifying some patients.

- The design of this clinical trial includes some restrictive eligibility criteria, which may favor the internal validity of the study but at the same time may compromise external validity.

- As some variables could affect the effect of our intervention, the study has used two strategies to control confounding. Firstly, the design includes randomization that aims at a similar distribution of variables in both groups different from the variable in study. Secondly, a multivariate analysis will be performed to adjust the effect of the intervention to those variables that could be different between the groups.

- In order to avoid as much as possible interobserver variability in the assessment of endoscopic lesions we have used two strategies. On the one hand, endoscopic assessment and Rutgeerts score will be discussed with all investigators in order to unify criteria. On the other hand, 3 images of ileocolonoscopy will be recorded from each patient in each center and will be reviewed by the reference center, the sponsor center.

10. ETHICAL AND ADMINISTRATIVE ASPECTS

10.1. COMPLIANCE WITH REGULATORY REQUIREMENTS

This clinical trial will be conducted in compliance with the protocol and all regulatory requirements, in accordance with Good Clinical Practice (GCP), including International Conference on Harmonization (ICH) Guidelines and in accordance to human rights and to the medical ethics defined on the World Medical Association Declaration of Helsinki of "Ethical Principles for Medical Research Involving Human Subjects" of 2013.

10.2. INSTITUTIONAL REVIEW AND APPROVAL

This clinical trial is also designed in accordance to *Ley 29/2006, de 26 de Julio, de garantías y uso racional de medicamentos y productos sanitarios* and to *Real Decreto 223/2004, de 6 de Febrero, por el que se regulan los ensayos clínicos con medicamentos*. Before the initiation of this study it is required the informed approval by the *Comitè ètic d'investigació Clínica* (CEIC) and its conformity in each participating hospital, and the authorization for the study itself by the *Agencia Española del Medicamento y Productos Sanitarios* (AEMPS). This study cannot be initiated until a copy of the document for its authorization has been obtained, as required by the applicable legislation. The Principal Investigator is responsible for notifying about the progress of the study, any changes made and all unanticipated risks that occur during its performance.

This clinical trial will be registered in the EUDRA-CT as well as in the Spanish Register (reec.aemps.es) and in clinicaltrials.gov.

10.3. INFORMED CONSENT

All the subjects participating in this clinical trial will be adequately informed on the voluntariness of their participation and that they are also free to withdraw from it at any time without prejudice to their treatment. Before the start of this study, all information related to the aims, methods and the possible benefits and adverse events that can arise from it will be given in understandable terms. All the subjects will have signed the informed consent to participate in the study before taking part of it (ANNEX 11). The specific information and informed consent for the performance of an ileocolonoscopy at

24 weeks of therapy will follow the normal healthcare process, as it forms part of the current clinical practice.

10.4. SUBJECTS ANONYMITY AND CONFIDENTIALITY

Investigators and other study staff will ensure the anonymity of identifying information at every moment by codes that will correspond to identification data of each subject. All data and documents will be properly disposed, and access to identifiable information will be limited. The Monitor of the study and regulatory authorities will be granted access to the original medical records of each patient for the verification of clinical trial procedures and data collection, without any violation of their confidentiality.

In any presentation of the results of this clinical trial (meetings, congresses, publications) personal information will remain always confidential.

Confidentiality of personal data of participants will be in accordance to *Ley 15/1999, de 13 de Diciembre, de Protección de Datos de Carácter Personal.* Additionally, the subject can access, rectify, oppose and cancel his/her personal data at any time in this study.

10.5. CASE REPORT FORM AND SOURCE DOCUMENTS

A Case Report Form (ANNEX 8) will be used, electronically, to record all participant data specified by the present protocol. Source documents, this is, the original results of observations and activities performed by investigators, may include laboratory data, drug accountability records, study progress notes and others, and must be maintained by the Investigators and be available for inspection by the Monitor and regulatory authorities.

10.6. CIVIL LIABILITY INSURANCE

The study has a civil liability insurance that will take the responsibility towards its members and will grant specific cover for any damage that occurs as a consequence of the study.

11. PRACTICAL CONSIDERATIONS

11.1. MULTICENTRICITY

Based on hospital registers, in 1 year the number of patients with CD undergoing a bowel resection ranges from 10 to 30, depending on centers. Taking into consideration that our study has established some restrictive criteria we can assume that, approximately, 5 to 7 patients could meet our criteria each year in a single hospital. We have estimated a needed sample size of 132 in total.

With all these considerations in mind, we propose a multicenter clinical trial with 12 different participating hospitals of Spain and a recruitment period of 3 years in order to ensure the attainment of the sample size.

11.2. RESPONSIBILITIES OF THE SPONSOR AND THE PRINCIPAL INVESTIGATOR

The Sponsor, at the same time the Principal Investigator of the study, is responsible for:

- Initiating, managing and ensuring the funding and adequate resources for the study.
- Ensuring the obtainment of all the necessary approvals from the appropriate regulatory agency (AEMPS) and ethics review (CEIC).
- Selecting the investigators and provide them the appropriate information to ensure that this protocol is adequately conducted.
- Ensuring the appropriateness of each collaborating center.
- Ensuring the supply of active treatment and the identical placebo formulation to each participating hospital.
- Designating a Monitor for this clinical trial.
- Publishing the results, positive or negative, of this study.

Sponsor of this clinical trial can stop its performance at any time because of protocol violation or safety issues, and can stop the participation of a subject because of particular violation of this protocol, adverse events or because of the choice of patient.

11.3. RESPONSIBILITIES OF THE MONITOR

The Monitor will act as a link between the Sponsor and the Principal Investigator of each participating hospital, being responsible for:

- Ensuring the appropriate recruitment of patients according to eligibility criteria and the obtainment of their informed consent.
- Monitoring and verifying the adequateness of the clinical trial. This also includes verifying that all data collected in Case Report Form is correct and complete according to source documents.
- Establishing a good communication between the Sponsor and each participating center.
- Monitoring the distribution and devolution of the treatments of the study.

11.4. RESPONSIBILITIES OF THE COORDINATOR INVESTIGATOR

An investigator of the sponsor center will act as the Coordinator Investigator of this multicenter clinical trial, being responsible for acquainting all investigators and all participating staff with all the procedures that will take place. This includes newsletters by email and teleconference and in person coordination meetings along the study.

11.5. ELIGIBILITY OF COLLABORATING CENTERS

Collaborating centers have to meet the following criteria In order to ensure the appropriateness of their participation:

- Previous experience on research.
- Presence of a Gastrointestinal Surgery Department, Gastroenterology Service and an adequate ileocolonoscopy setting.
- Physicians experienced in inflammatory bowel disease and endoscopy.

11.6. RESPONSIBILITIES OF INVESTIGATORS AND PARTICIPATING STAFF

Each hospital will designate a Principal Investigator that will be responsible for:

- Conducting this clinical trial in accordance with its protocol and the established plan.
- Ensuring the adequate recruitment of participants and their informed consent.
- Ensuring that the study is being performed in accordance with ethical principles and all local laws. Ensuring that the rights of each subject of the study are protected.
- Ensuring an adequate data collection and recording.
- Notifying adverse or unexpected events that occur during the study.

Nursing service will also participate in this clinical trial. The Pharmacy Service will be responsible for preparation, safekeeping, reception and dispensation of treatment, as well as the control and traceability of medications.

12. WORK PLAN AND CHRONOGRAM SCHEME

This clinical trial is predicted to be performed in 5 years that will be organized in the following phases:

1. COORDINATION PHASE (6 months) [Sponsor, all investigators and collaborators]:

1.1. Setting-up: in this period it will be performed the approach and selection of hospitals participating in the clinical trial, with the initial idea and protocol.

1.2. In person meeting (1): a first in person meeting will take place with all investigators of each hospital in order to explain the project design and execution plan. Details will be discussed in order to ensure homogeneity in all centers. The Coordinator Investigator will explain the system and procedures of recruitment, randomization, dispensation of therapy, data management and cleaning and central data monitoring. Among all the clinical trial, regular feedback will be provided to each hospital participating in this study and adequate methods of communication will be established.

1.3. Analytical framework establishment.

1.4. Final project design.

1.5. Project evaluation and approval: by AEMPS and CEIC.

2. PATIENT INCLUSION, EVALUATION AND DATA COLLECTION PHASE (43 months) [Sponsor, all investigators and collaborators]:

2.1. Subjects recruitment period: during this phase it will take place the inclusion of patients from January of 2015 to December of 2017. Patients will be included from each hospital until the sample size is achieved.

2.2. Subjects evaluation period: at the same time patients evaluation period will be performed applying the same visit chronogram to all participants. The evaluation period will end 24 weeks (trial endpoint) after the inclusion of the last subject.

2.3. Data entry and processing: data will be entered in the database according to the established protocol and Case Report Form for each patient. Data collection will be

finished in the next month after ending evaluation period. Within all this period the Monitor will perform controls to ensure adequate data collection.

2.4. Teleconference meetings (2, 3, 4 and 5): the Coordinator Investigator will ensure motivation and internal collaboration of all participating staff during the study. The first teleconference meeting (2) will aim at reviewing endoscopic and clinical criteria in order to ensure the maximum homogeneity as possible in evaluation of participants. There will be three additional teleconference meetings (3-5) in order to ensure recruiting, the quality and homogeneity of data collection and to discuss the progress of the clinical trial.

3. DATA ANALYSIS PHASE (3 months) [Sponsor, all investigators and statistical consultant]:

3.1. Statistical analysis monitoring: two statistical analysis will be performed along the study in order to control its progress (last trimester of 2015 and second one of 2017).

3.2. Final statistical analysis: final analysis will be performed at the end of the study when all data have been collected.

4. FINALIZATION PHASE (4 months) [Sponsor and all investigators]

4.1. Interpretation of results: results will be analyzed and investigators will perform the final discussion and conclusions of the clinical trial.

4.2. In person meeting (6): there will be a last meeting in November of 2018 in order to discuss the findings as a collaborative group.

4.3. Final report elaboration.

5. PUBLICATION AND DISSEMINATION PHASE (4 months) [Sponsor and all investigators]:

It is predicted that the findings of this clinical trial will be published and disseminated, as a collaborative group, in journal articles, reports, conference presentations and others. As a multicenter clinical trial, each investigator can be responsible for local dissemination. It is also predicted a presentation of results in the annual congress of AEG (*Asociación Española de Gastroenterología*).

Year	2014						2015				2016				2017				2018										2019			
Month/months of the year (in numbers)	7	8	9	10	11	12	1 2 3	4 5 6	7 8 9	10 11 12	1 2 3	4 5 6	7 8 9	10 11 12	1 2 3	4 5 6	7 8 9	10 11 12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4
ACTIVITY																																		
1. COORDINATION PHASE																																		
Setting up																																		
In person meeting (1)																																		
Analytical framework																																		
Final project design																																		
Project evaluation and approval																																		
2. PATIENT INCLUSION, EVALUATION AND DATA COLLECTION PHASE																																		
Subjects recruitment period																																		
Subjects evaluation period																																		
Data entry and processing																																		
Teleconference meetings (2-5)																																		
3. DATA ANALYSIS PHASE																																		
Statistical analysis monitoring																																		
Final statistical analysis																																		
4. FINAL REPORT PHASE																																		
Interpretation of results																																		
In person meeting (6)																																		
Final report elaboration																																		
5. PUBLICATION AND DISSEMINATION PHASE																																		
Articles, meetings, conferences																																		
Annual congress of AEG																																		

13. BUDGET

Physicians and nurses that will visit and assess patients in each participating hospital will form part of the study staff and only interventions that are additional to the current clinical practice are considered in the following estimated budget:

ITEM	Cost per unit	Number of units	Total cost
STAFF			
Study Monitor (partial time)	10.000€/year	1 person	
			x 4years
			40.000€
Statistical consultant	35€/hour	1 person	
			x 90hours
			3.150€
Placebo formulation	10,30€/hour	1 person	
			x 3hours
			30,9€
		SUBTOTAL	**43.180,9€**
TREATMENT			
Experimental group (PVL[1])			
SC Methotrexate, 25mg	20,25€/unit	24 units/patient	486€/patient
Oral folic acid, 5mg	0,10€/unit	24 units/patient	2,4€/patient
			x 66patients
			32.234,4€
Control group			
SC placebo	0,0367€/unit	24 units/patient	0,88€/patient
Oral placebo	0,02€/unit	24 units /patient	0,48€/patient
			x 66patients
			89,76€
		SUBTOTAL	**32.324,16€**
ASSESSMENT AND MONITORING			
Tests and Chest X-Ray at visit 1	150,56€/unit	1/patient	150,56€/patient
			x 132 patients
			19.873,92€
Pregnancy urine test	10€/unit	1/patient	10€/patients
			x 66patients
			660€
Monitoring blood tests	40,30€/unit	3/patient	120,9€/patient
			x 132patients
			15.958,8€
		SUBTOTAL	**36.492,72€**
STUDY INSURANCE			
Total cost			22.420€
		SUBTOTAL	**22.420€**
MEETINGS, PUBLICATIONS AND TRAVEL COSTS			
BMC Gastroenterology	(Article-processing charges)		**1.675€**
Coordination in person meetings			
Food and miscellanea	200€/unit	1unit/meeting	200€/meeting
Transport	85€/journey	10 investigators	850€/meeting
			x 2meetings
			2.100€
Annual Congress (AEG)			
Transport, stay and inscription	545€/person	2 investigators	**1.090€**
		SUBTOTAL	**4865€**
		TOTAL COST	**139.282,78€**

[1]PVL: *Precio de Venta de Laboratorio*

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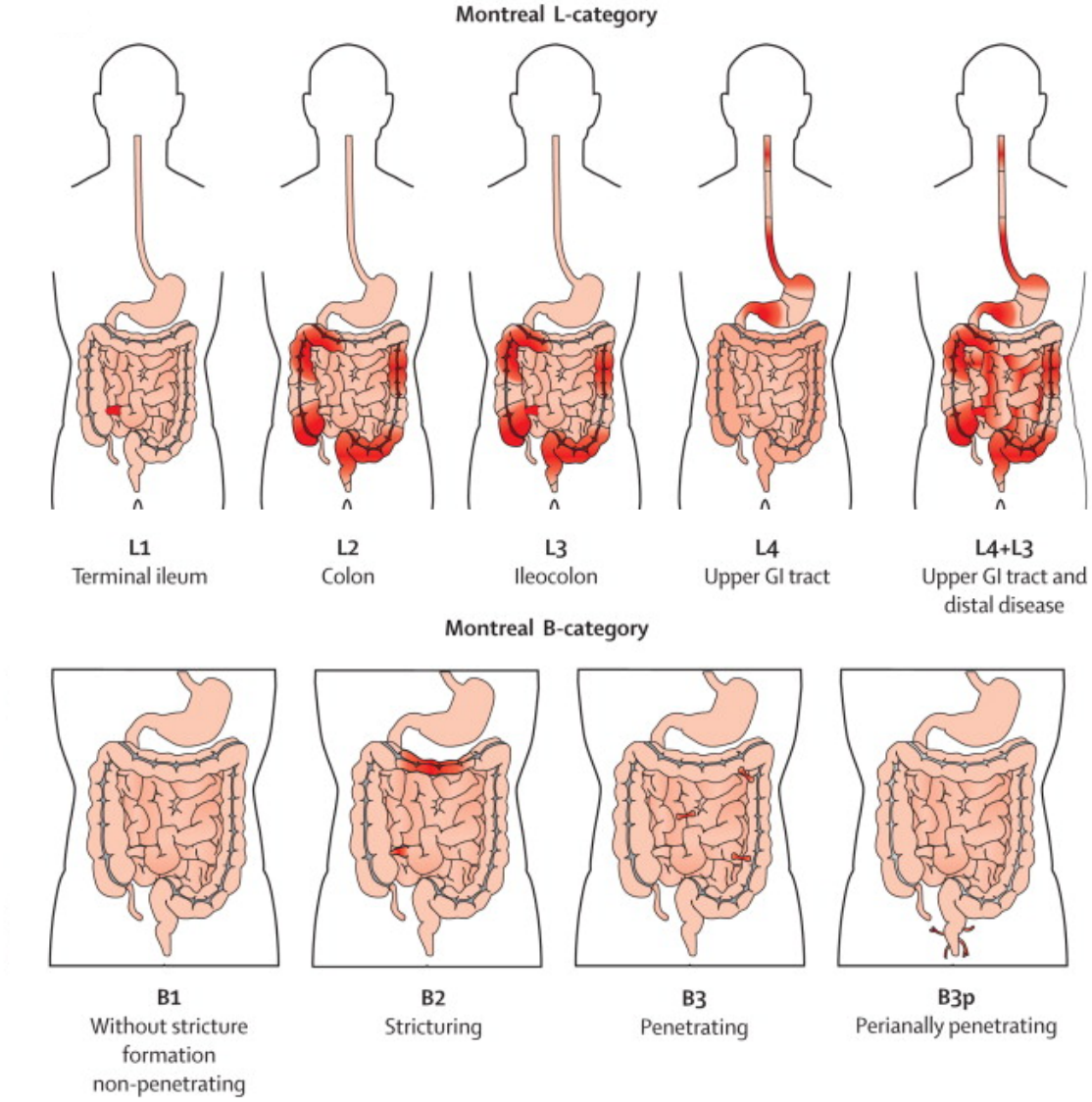
15. ANNEXES

ANNEX 1: MONTREAL CLASSIFICATION FOR CROHN'S DISEASE

Montreal classification for Crohn's disease		
Age at diagnosis (A)	**Location (L)**	**Behavior (B)**
A1: ≤ 16 years	**L1:** ileal	**B1:** non-structuring, non-penetrating (inflammatory)
A2: 17-40 years	**L2:** colonic	**B2:** structuring (obstructive)
A3: >40 years	**L3:** ileocolonic	**B3:** penetrating (fistulizing)
	L4: upper gastrointestinal (GI) disease	
	"**L4**" can be added, as a modifier, to L1-L3 if concomitant upper GI disease is present	"**p**" (perianal disease modifier) is added to B1-3 when concomitant perianal disease is present



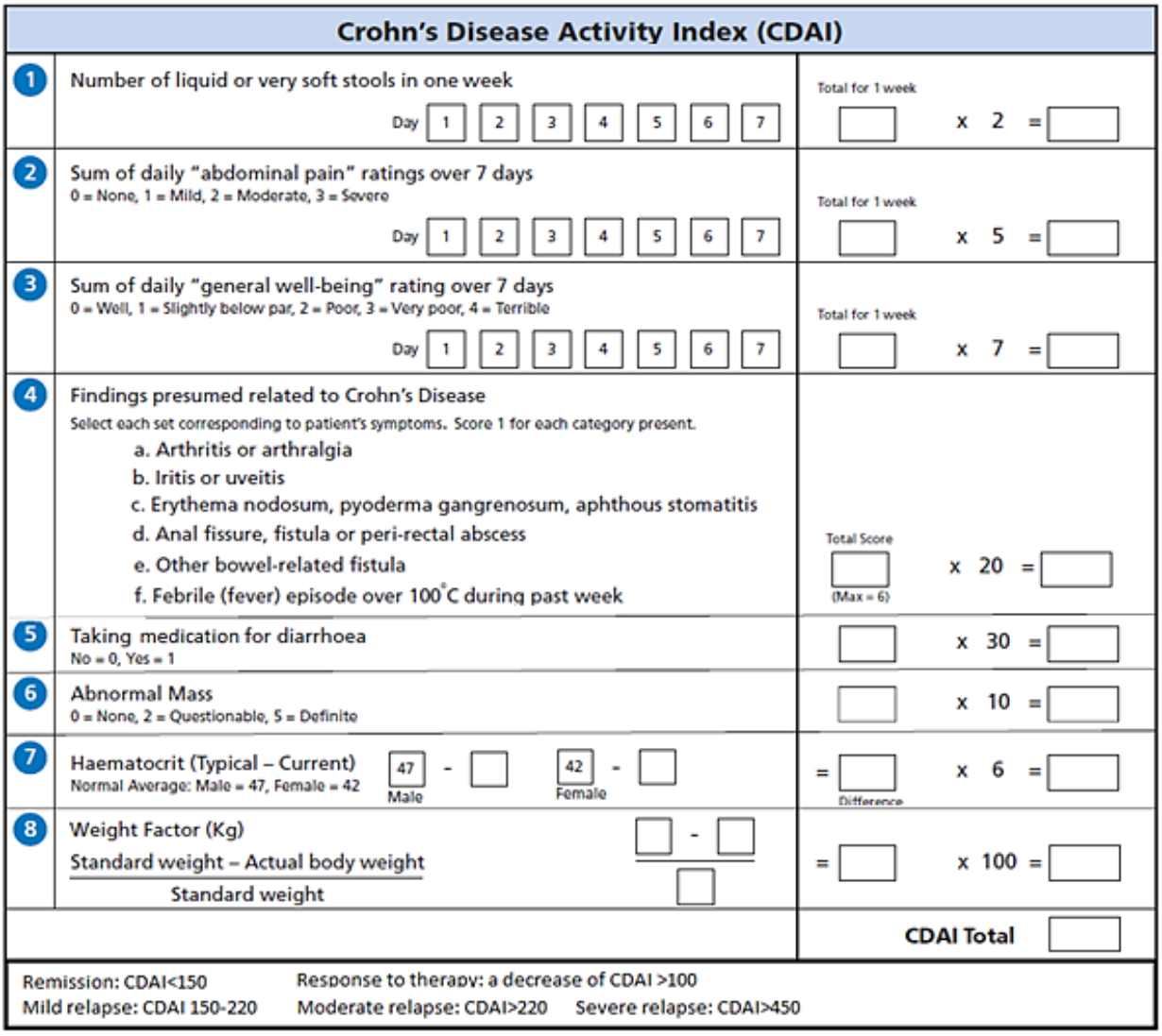
Adapted from: Baumgart DC, Sandborn WJ. Crohn's disease. Lancet [Internet]; 2012 Nov 3 [cited 2014 Jul 11];380(9853):1590–605. Available from: http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(12)60026-9/fulltext

ANNEX 2. LENNARD-JONES DIAGNOSTIC CRITERIA FOR CROHN'S DISEASE

Lennard-Jones diagnostic criteria for Crohn's disease				
	Examination or endoscopy	Radiology	Biopsy	Surgical specimen
Proximal lesions	+	+	+	+
Anal lesions	+		+	+
Segmentary distribution	+	+	+	+
Fissure		+		+
Abscess	+	+		+
Fistula	+	+		+
Stenosis	+	+		+
Pathology findings				
- Ulcers			+	+
- Lymphoid aggregates			+	+
- Granulomas			+	+
Diagnosis of Crohn's disease if established if: (1) Granuloma is found at pathological examination + 1 other criteria (2)In the absence of granuloma: 3 criteria Probable disease is defined by 2 criteria in the absence of granuloma				

Adapted from: Nos Mateu P, Clofent Vilaplana J. Enfermedad de Crohn. In: Ponce García J, editor. Tratamiento de las enfermedades gastroenterológicas [Internet]. 3rd ed. Madrid: Asociación Española de Gastroenterología; 2011. p. 293–304. Available from: www.manualgastro.es/ei/ctl_servlet?_f=1036&id_contenido=709

ANNEX 3. CROHN'S DISEASE ACTIVITY INDEX (CDAI)

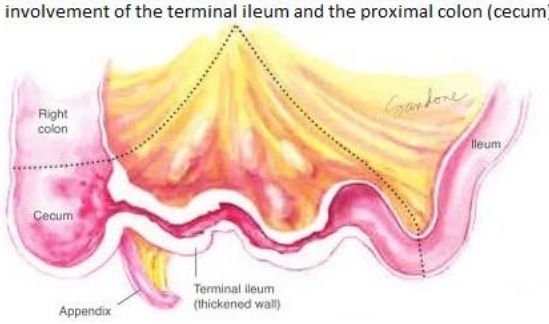


Adapted from:South African Gastroenterology [Internet]. Mowbray: SAGES; 2014. Crohn's Disease Patient Assessment Sheet; 2014 [cited 2014 Oct 24]; Available from: www.sages.co.za/images/CDAI%20SCORE%20SHEET.pdf

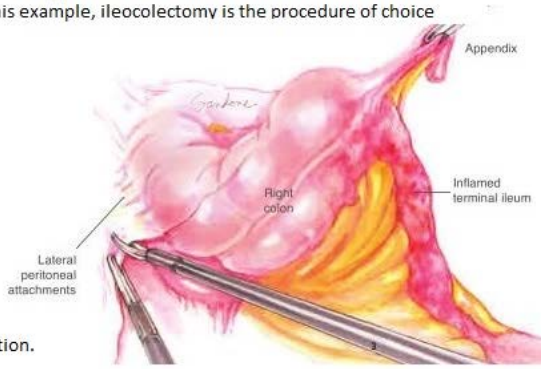
ANNEX 4. ILLUSTRATIONS OF SURGERY AND RECURRENCE OF CROHN'S DISEASE

Example of a first surgery in Crohn's disease:

1. The most common pattern of disease at initial presentation is involvement of the terminal ileum and the proximal colon (cecum)

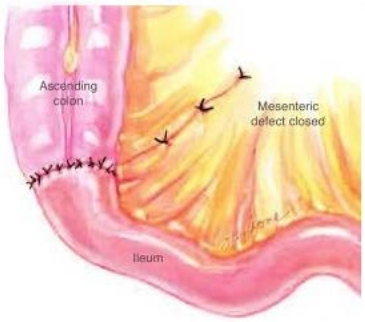


2. The vast majority of patients with Crohn's disease eventually require surgical resection with ileocolic anastomosis. In this example, ileocolectomy is the procedure of choice

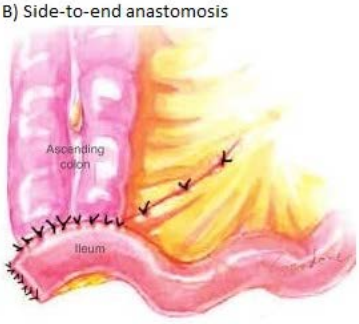


3. Either a hand-sewn or stapled anastomosis can be performed after resection. Here we show the 3 alternatives to perform the intestinal anastomosis:

A) End-to-end anastomosis



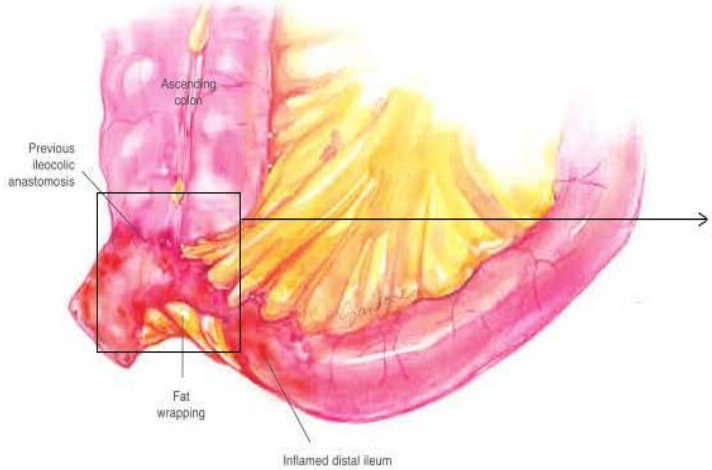
B) Side-to-end anastomosis



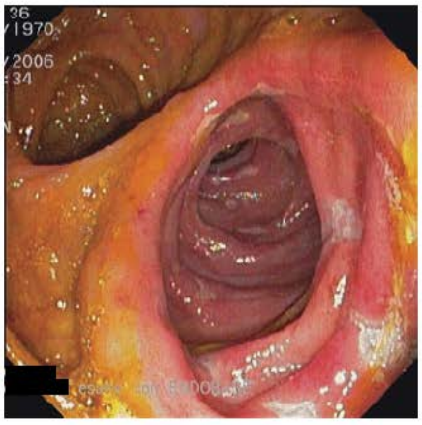
C) Side-to-side anastomosis

Example of postoperative recurrence at anastomosis and neoterminal ileum:

4. Following surgery, recurrence of Crohn's disease is the norm. Frequently, lesions will recur in the ileum just proximal to the ileocolic anastomosis performed in the first surgery



5. Endoscopic view of the ileocolonic anastomosis 1 year after surgery, showing diffuse and deep ulcerations of the neoterminal ileum with no stenosis (Rutgeerts score: i4)



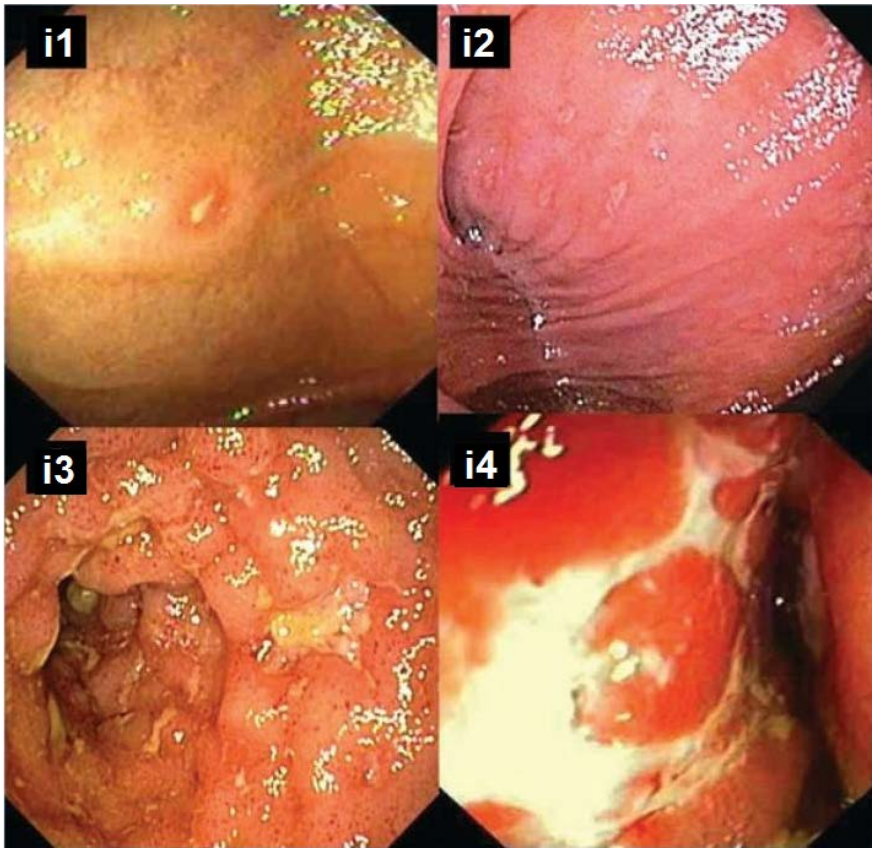
Illustrations and text (1-4) are adapted from: Cameron JL, Sandone C. Atlas of Gastrointestinal Surgery, Volume 2. 2nd ed. Shelton, CT: PMPH-USA; 2014 .

Endoscopic image (5) is taken from: Biancone L, Sica GS, Calabrese E, Onali S, Petruzziello C, Pallone F. Frequency and pattern of endoscopic recurrence in Crohn's disease patients with ileocolonic resection using a laparoscopic versus laparotomic approach: a prospective longitudinal study. Am J Gastroenterol [Internet]. The American College of Gastroenterology; 2008 Mar [cited 2014 Oct 25];103(3):809–11. Available from: http://www.nature.com/ajg/journal/v103/n3/full/ajg200850165a.html

ANNEX 5. RUTGEERTS ENDOSCOPIC RECURRENCE SCORE AND ENDOSCOPIC IMAGES

Rutgeerts endoscopic recurrence score	
Endoscopic score	**Definition**
i0	No lesions
i1	≤5 aphthous lesions
i2	>5 aphthous lesions with normal mucosa between the lesions, or skip areas of larger lesions or lesions confined to the ileocolonic anastomosis
i3	Diffuse aphthous ileitis with diffusely inflamed mucosa
i4	Diffuse inflammation with already larger ulcers, nodules and/or narrowing

i0 and i1 imply endoscopic remission while i2, i3 and i4 imply recurrent endoscopic disease



Adapted from: Hashash JG, Regueiro MD. The evolving management of postoperative Crohn's disease. Expert Rev Gastroenterol Hepatol [Internet]. 2014 [cited 2014 Oct 21];6(5):637–48.
Available from: http://www.medscape.com/viewarticle/772973_1

ANNEX 6. RELEVANT INFORMATION ABOUT METHOTREXATE

Presentation: 1 pre-filled syringe that contains 25mg of methotrexate (MTX)

Pharmaceutical form: transparent, yellow to brown, injectable solution with a pH of 7.0-9.0

General advertences:

- MTX should be used with caution in patients with renal failure.
  Dosage adjustment *(Creatinine clearance (ml/min): % dose):* >50:100%; 20-50:50%;
- MTX should be used with caution in patients with liver failure, and only if needed.
- Patients need to be advised that MTX has to be injected only once a week in a fixed day.
- Folic acid supplementation is recommended.

Fertility, pregnancy and breastfeeding:

Reproductive toxicity is especially important during the first trimester. MTX is teratogenic: it can produce fetal death and/or congenital anomalies. Women at fertile age have to undergo a pregnancy test before starting this therapy. During the treatment, men and women at fertile age have to use contraceptive methods and at least for the following 6 months after its use. MTX is excreted by breast milk and can produce toxicity. Thus, this therapy is contraindicated during breastfeeding.

Contraindications of methotrexate

- Known hypersensitivity to MTX or to any of its excipients
- Liver failure, alcoholism, alcoholic liver disease or other chronic liver disease.
- Bilirubin >5mg/dl
- Renal failure (creatinine clearance <20ml/min)
- Hematologic dyscrasia (aplastic anemia, leukopenia, thrombocytopenia and significant anemia).
- Severe acute or chronic infections as tuberculosis and HIV, oral ulcers and GI ulcerative disease.
- Pregnancy and breastfeeding.
- Concurrent vaccination with live vaccines (which contain live attenuated microorganisms).

Adverse effects

- Subcutaneous administration has a good local tolerability and it has only been reported the apparition of mild cutaneous reactions, which decrease with time of treatment.
- Adverse effects of methotrexate are summarized in the following tables:

Adverse effects of methotrexate					
	Very frequent ≥1/10	**Frequent ≥1/100, <1/10**	**Infrequent ≥1/1.000, <1/100**	**Rare ≥1/10.000, <1/1.000**	**Very rare <1/10.000**
Infections					Sepsis, opportunistic infections (sometimes with risk of death), cytomegalovirus infection
Neoplasms (cysts and polyps included)			Individual cases of lymphoma (possible remission). Controversial association of MTX with lymphoma		
Blood, lymphatic and immune system		Leukopenia, thrombopenia, anemia	Pancytopenia, agranulocytosis, hematopoietic disorders	Megaloblastic anemia	Bone marrow suppression, aplastic anemia, lymphadenopathies, lymphoproliferative disorders (partially reversible), eosinophilia,neutropenia. Immunosuppression, hypogamma-globulinemia
Psychiatric					Insomnia
Nervous system		Headache, fatigue, somnolence	Vertigo, confusion, depression, convulsions	Severe vision alterations, mood changes	Pain, asthenia, paresthesia, metallic taste, meningismus, acute aseptic meningitis
Ocular				Visual disorders	Conjunctivitis, retinopathy
Cardiovascular				Pericarditis, pericardial effusion, pericardial tamponade, hypotension, thromboembolic phenomena	

Adverse effects of methotrexate (*continuation*)					
	Very frequent ≥1/10	**Frequent ≥1/100, <1/10**	**Infrequent ≥1/1.000, <1/100**	**Rare ≥1/10.000, <1/1.000**	**Very rare <1/10.000**
Respiratory		Acute interstitial pneumonitis (independently of doses of MTX)	Pulmonary fibrosis	Pharyngitis, apnea, asthma	Pneumonia by *Pneumocystis carinii*, chronic obstructive pulmonary disease
Gastrointestinal	Loss of appetite, nausea, vomiting, abdominal pain, oral and throat ulcers, dyspepsia	Diarrhea (specially within 24-48h after administration)	GI ulcers and hemorrhages	Gingivitis, malabsorption, enteritis, melena	Hematemesis, toxic megacolon
Hepatobiliary	increased liver enzymes (AST, ALT, alkaline phosphatase and bilirubin)		Fatty liver degeneration, fibrosis, cirrhosis; diabetic metabolism, decreased serum albumin	Acute hepatitis, hepatotoxicity	Chronic hepatitis reactivation, acute liver degeneration, liver failure
Skin and subcutaneous tissue		Exanthema, erythema, pruritus	Urticaria, photosensitivity, skin hyperpigmentation, hair loss, herpes zoster; vasculitis, Steven-Johnson and Lyell Syndromes	Increased nail pigmentation, acne, petechial rash and ecchymosis, erythema multiforme.	Acute paronychia, furunculosis, allergic vasculitis, hydrosadenitis, telangiectasia, disseminated herpes simplex and mycose
Musculo-skeletal and connective tissue			Arthralgia, myalgia, osteoporosis	Bone fractures	
Kidneys and urinary tract			Urinary bladder ulcers, hematuria, dysuria	Renal failure, oliguria and anuria	Proteinuria
Reproductive system			Vagina inflammation and ulceration		Loss of libido, impotence, infertility, oligospermia, menstrual disorders,
General disorders			Severe allergic reactions, anaphylactic shock		Fever, alteration of cicatrization process

All this information of methotrexate has been summarized and adapted from:

Ficha Técnica de Metotrexato [Internet]. Madrid: Agencia Española del Medicamento y Productos Sanitarios; 2011. Available from: http://www.aemps.gob.es/cima/pdfs/es/ft/77223/FT_77223.pdf

ANNEX 7. VISITS CHRONOGRAM

	Pre-OP approach	**Intervention (start)**							**POR EVALUATION**
Number of visit	1	2	3	4	5	6	7	8	9
Number of week	**-2**	**0**	**2**	**6**	**10**	**14**	**18**	**22**	**24**
Days (+/-2)	-14 to -1	1	15	43	71	99	127	155	169
Informed consent	x								
Px number assignation	x								
Px treatment allocation		x							
Eligibility criteria verification	x	x							
Treatment explanation	x	x							
CH and demographic data	x								
Concomitant Treatments	x	x	x	x	x	x	x	x	x
Confirm nonsmoker px	x	x	x	x	x	x	x	x	x
Chest radiograph	x								
Physical examination[1]	x	x	x	x	x	x	x	x	x
Blood tests[2]	x		x	x	x	x	x		x
Ileocolonoscopy explanation and informed consent								x	
Pregnancy urine test	x								
Ileocolonoscopy									x
CDAI evaluation[3]	Instruction	x				x			x
Adverse events			x	x	x	x	x	x	x
Adherence to treatment (dispensation/return)[4]		x	x	x	x	x	x	x	x

CH: clinical history; Px: patient; Pre-op: preoperative; POR: postoperative recurrence;

[1] Physical examination: complete examination at each visit, including measurement of vital constants and weight.

[2] Blood tests: including full hemogram, glucose levels, kidney function tests, liver function tests and CRP.

*Hepatitis B and C serology, HIV serology and Mantoux test will be performed at visit 1.

[3] CDAI: at the first visit (preoperative approach) patients will be just instructed about the need of recording the first 3 components of CDAI with a model given in paper (ANNEX 3) for the 7 days before the next visit.

[4] Adherence to treatment: in order to ensure adequate adherence, the Pharmacy Service of each hospital will be responsible for dispensation of the medication to each patient according to their group allocation. At the same moment, patients will return syringes and blister pack (dispensation/return method). As physicians will visit the patient the same day, subjects will be asked about their adherence, reasons of missed doses (when no compliance) and adverse effects.

ANNEX 8. CASE REPORT FORM

CASE REPORT FORM

Participant Study Number:

DEMOGRAPHIC DATA AND CRITERIA FOR INCLUSION

Date of birth:

Sex: M ☐ F ☐ Negative pregnancy urine test (visit 1) ☐

Age at onset of Crohn's disease: _____ **First resection:** Yes ☐No ☐ **Age at resection:** _____

Family history of IBD: Yes ☐ No ☐

Prior medication: Antibiotics ☐ Mesalazine ☐ Thiopurines ☐ MTX ☐ anti-TNF ☐

Location of Crohn's disease (L): L1 ☐ L2 ☐ L3 ☐ L4 ☐

Behavior of disease (B): B1 ☐ B2 ☐

SURGERY AND ANATOMICAL PATHOLOGY DATA

Length of resected segment (cm): _____

Type of anastomosis: Side-to-end ☐ Side-to-side ☐ End-to-end ☐

Postoperative complications: Yes ☐ No ☐

Disease present at resection margins: Yes ☐ No ☐

Granuloma at resection specimen: Yes ☐ No ☐

Myenteric plexitis at resection specimen: Yes ☐ No ☐

PATIENT FOLLOW-UP

- **CLINICAL AND PHYSICAL EVALUATION:**

Visit (specify date)	Smoking habit	Concomitant treatments	Physical examination	Vital constants	Weight	CDAI (2,6,9)
1						
2						
3						
4						
5						
6						
7						
8						
9						

- **TREATMENT AND SAFETY MONITORING:**

Chest X-Ray (visit 1): No ☐ Yes ☐ **Results**: Normal☐ Lesions☐ (specify)_____

Mantoux test (visit 1): (-)☐ (+)☐ **HIV Serology** (visit 1): (-)☐ (+)☐

HBV Serology (visit 1): (-)☐ (+)☐ **HCV Serology** (visit 1): (-)☐ (+)☐

BLOOD TESTS: (component/number of visit)

	1	3	4	5	6	7	9
(Specify date of extraction)							
HEMOGRAM							
Erythrocytes (M/mcL)							
Hemoglobin (g/dL)							
Hematocrit (%)							
MCH (fL)							
MCHC (g/dL)							
Platelet count(K/mcL)							
WBC (k/mcL)							
WBC FORMULA (% and K/mcL)							
Neutrophils							
Lymphocytes							
Monocytes							
Eosinophils							
Basophils							
BIOCHEMISTRY							
Glucose (mg/dL)							
Urea (mg/dL)							
Creatinine (mg/dL)							
Glomerular filtration CKD-EPI formula(mL/min)							
C-reactive protein							
Na+ (mEqu/L)							
K+ (mEqu/L)							
Total bilirubin(mg/dL)							
Direct bilirubin (mg/dL)							
Indirect bilirubin (mg/dL)							
Albumin (g/dL)							
AST (U/L)							
ALT (U/L)							
GGT (U/L)							
Alkaline Phosphatase (U/L)							

ALT: alanine aminotransferase: APTT:Activated Partial Thromboplastin Time; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; MCHC: mean corpuscular hemoglobin concentration; MHC:mean corpuscular hemoglobin; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus WBC: white blood cells

- **Adverse events:** (Visit/occurrence)

	No	Yes	Specify type and duration
3	☐	☐	_
4	☐	☐	_
5	☐	☐	_
6	☐	☐	_
7	☐	☐	_
8	☐	☐	_
9	☐	☐	_

- **Adherence to treatment:**

	Yes	No	Number of doses	Reasons for discontinuation	Information from Pharmacy Service (dispensation/return)
3	☐	☐			
4	☐	☐			
5	☐	☐			
6	☐	☐			
7	☐	☐			
8	☐	☐			
9	☐	☐			

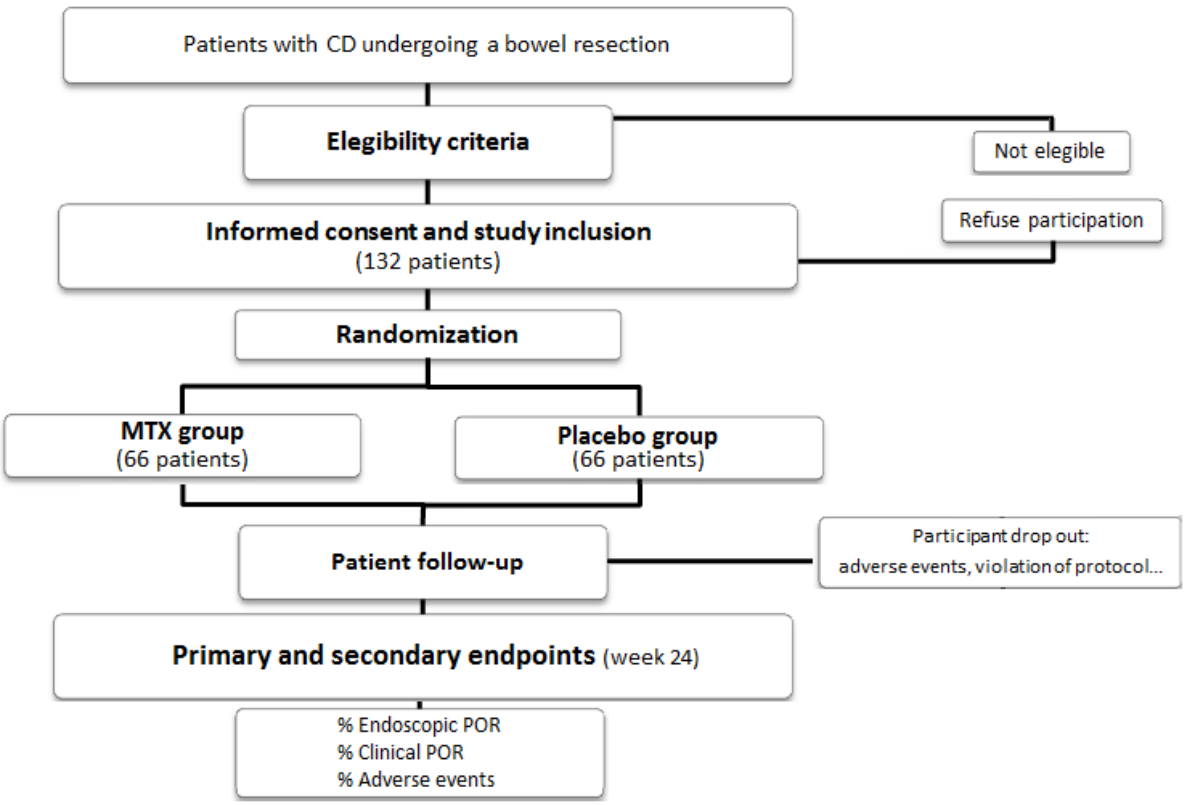
- **ILEOCOLONOSCOPY** (visit 9)**:**

Endoscopic recurrence: No ☐
Yes ☐

Specify Rutgeerts score: _____

Ileocolonoscopy images:

ANNEX 9. STUDY SCHEME



ANNEX 10. STATISTICAL ANALYSIS APPROACH

Table 1. Base-line characteristics

Variable	MTX (n=66)	Placebo (n=66)	p value*
Sex			
Age (years)			
Age at onset of CD (years)			
Age at resection (years)			
Family history			
Weight (Kg)			
Location of CD (L1/L2/L3)			
Prior antibiotics			
Prior mesalazine			
Prior thiopurines			
Prior methotrexate			
Prior anti-TNF			
Length of resection (cm)			
Anastomosis (S-S,E-E,S-E)			
Postoperative complications			
Granuloma at resection specimen			
Myenteric plexitis at resection specimen			
Disease at resection margins			

Table 2.Analysis of potential confounding factors

Variable	No recurrence	Recurrence	p value*
Sex			
Age (years)			
Age at onset of CD (years)			
Age at resection (years)			
Family history			
Weight (Kg)			
Location of CD (L1/L2/L3)			
Prior antibiotics			
Prior mesalazine			
Prior thiopurines			
Prior methotrexate			
Prior anti-TNF			
Length of resection (cm)			
Anastomosis (S-S,E-E,S-E)			
Postoperative complications			
Granuloma at resection specimen			
Myenteric plexitis at resection specimen			
Disease at resection margins			

Effect of the intervention:

Table 3. Endoscopic recurrence

	POR (%)	No POR (%)	P	RR (CI 95%) Non-adjusted	RR (IC 95%) Adjusted*
MTX					
Placebo					

Table 4. Clinical recurrence

	POR (%)	No POR (%)	P	RR (CI 95%) Non-adjusted	RR (IC 95%) Adjusted*
MTX					
Placebo					

Table 5. Adverse events (description)

Adverse effect (type)	MTX (%)	Placebo (%)

ANNEX 11. INFORMATION SHEET AND INFORMED CONSENT (SPANISH AND CATALAN):

HOJA DE INFORMACIÓN AL PACIENTE

Título del estudio:

Eficacia del tratamiento con metotrexato para la prevención de la recurrencia postquirúrgica en la enfermedad de Crohn.

Ensayo clínico multicéntrico a doble ciego y controlado con placebo sobre la eficacia de utilizar metotrexato como tratamiento preventivo de la recurrencia postquirúrgica de la enfermedad de Crohn.

Código del promotor:

Promotor:

Investigadores principales:

Centro:

Nos dirigimos a usted para informarle sobre el estudio de investigación al que se le invita a participar. Este estudio ha sido aprobado por el Comité Ético de Investigación Clínica (CEIC) de este hospital y la Agencia Española del Medicamento y Productos Sanitarios (AEMPS), en cumplimiento con la legislación vigente, el Real Decreto 223/2004, de 6 de Febrero, por el que se regulan los ensayos clínicos con medicamentos.

Antes de que decida acerca de su participación en este estudio, es importante que reciba y comprenda correctamente la información contenida en este documento. Por ello, es necesario que se tome su tiempo y lea detenidamente la siguiente información, que puede consultar con las personas que considere oportunas. Su médico le aclarará todas las dudas que puedan surgirle tras la explicación.

CONDICIONES DE PARTICIPACIÓN

Su participación en este estudio es totalmente voluntaria y puede decidir no participar o retirarse del mismo en cualquier momento, sin dar ninguna explicación. La decisión de no participar en este estudio o de retirarse una vez se haya incluido nunca afectará a sus derechos legales y éticos a recibir tratamiento: usted continuará recibiendo el tratamiento más adecuado para su enfermedad.

No obstante, si usted decide retirarse de este estudio, es importante que informe a su médico. De igual forma, su médico puede decidir retirarle del estudio en caso de no cumplir con el protocolo que se establece o si experimenta algún efecto secundario importante.

DESCRIPCIÓN DEL ESTUDIO

Objetivos del estudio

Se le ha ofrecido participar en este estudio porque padece enfermedad de Crohn y acaba de ser sometido a una resección intestinal. Con elevada frecuencia, reaparece la enfermedad, lo que se conoce como recurrencia postquirúrgica.

Este estudio tiene como objetivo valorar la eficacia (prevención de la recurrencia postquirúrgica, tanto en forma de lesiones vistas en la endoscopia como sintomática) y el perfil de seguridad (efectos secundarios) de utilizar metotrexato en la prevención de la recurrencia de la enfermedad.

Procedimientos del estudio

Se prevé la participación de 132 pacientes en este estudio, distribuidos en diferentes hospitales en España. Habrá dos grupos de intervención y cada uno constará de 66 pacientes.

Este estudio utilizará dos pautas de tratamiento, y a usted se le distribuirá de forma aleatoria para recibir una de las dos. Ni usted ni los investigadores que lo atiendan conocerá a qué grupo ha sido asignado:

- Metotrexato administrado vía subcutánea a dosis de 25mg, una vez por semana, durante 24 semanas, con un suplemento semanal de 5mg ácido fólico vía oral una vez por semana, durante 24 semanas.
- Placebo (sustancia sin principio activo farmacológico) de administración subcutánea, una vez por semana, durante 24 semanas, junto a otro placebo administrado vía oral una vez por semana, durante 24 semanas. Ambos placebos serán idénticos en apariencia, dosis y forma de administración que los fármacos correspondientes administrados en el otro grupo de tratamiento.

Metotrexato está comercializado en España y se utiliza en el tratamiento de enfermedades inflamatorias, como la artritis reumatoide, desde hace muchos años. Metotrexato se utiliza en la práctica clínica habitual como medicamento inmunosupresor de segunda línea en pacientes que no responden o que no toleran a otros fármacos, la azatioprina y la mercaptopurina, en la inducción y el mantenimiento de la remisión de la enfermedad de Crohn. Sin embargo, este fármaco no tiene autorizada la indicación para enfermedad de Crohn y se utiliza en lo que se conoce como "uso compasivo", es decir, es utilizado a pesar de no constar de la autorización para su uso en esta enfermedad porque se conoce que puede resultar beneficioso para el paciente.

Usted debe saber que aunque ya se han hecho estudios que probaban la eficacia del metotrexato en pacientes con enfermedad de Crohn, éste el primer ensayo clínico que evalúa su eficacia para la prevención de la recurrencia postquirúrgica de la enfermedad.

¿Qué deberá hacer si decide participar en este estudio?

Una vez iniciado el tratamiento, usted seguirá una serie de controles para garantizar un desarrollo correcto y seguro del estudio. Algunos de esos controles, como la realización de análisis de sangre o visitas médicas, se harían igualmente en su caso aunque no participase en este estudio, para el control de la evolución de la enfermedad tras la cirugía y más periódicamente en el caso de que tomase otra medicación para la prevención de la recurrencia postquirúrgica. De forma adicional, será visitado por su médico y se le practicarán análisis de sangre destinados a evaluar la seguridad del medicamento que estará recibiendo. También se le instruirá sobre cómo administrar el fármaco en una consulta con enfermería. A las 24 semanas del tratamiento (aproximadamente a los 6 meses) se le realizará un estudio endoscópico (colonoscopia con ileoscopia), para evaluar su evolución. Esta prueba forma parte también de la práctica clínica habitual fuera de este estudio.

Debe saber que metotrexato se administra por vía subcutánea para asegurar que el fármaco actúa de forma adecuada. Usted deberá cumplir con el tratamiento y lo administrará como le será indicado específicamente por un/a enfermero/a. Durante el estudio, no podrá tomar ciertos medicamentos y en caso de ser necesario, su médico le explicará los medicamentos que podría tomar. Usted deberá notificar cualquier otro tratamiento que esté tomando así como la posible aparición de efectos secundarios a su médico.

Todas las personas que participen en este estudio, tanto hombres como mujeres, deben utilizar métodos anticonceptivos adecuados desde el inicio del tratamiento y por un total de 12 meses. Metotrexato está totalmente contraindicado en el embarazo y lactancia por la toxicidad que podría producir.

Beneficios derivados de su participación en el estudio

Usted podría beneficiarse fuera de este estudio tanto de tratamiento preventivo de forma inmediata a la cirugía como de recibirlo únicamente en caso de que aparezcan lesiones en la endoscopia de control realizada a los 6 meses, según la práctica clínica actual. El motivo de este estudio es conocer si metotrexato resulta eficaz y seguro para prevenir la recurrencia postquirúrgica. Usted podría beneficiarse del tratamiento del estudio pero también es posible que no obtenga ningún beneficio. Con su participación usted está contribuyendo además a mejorar el conocimiento sobre el manejo terapéutico de este problema.

Riesgos derivados de su participación en el estudio

Debe conocer que la administración subcutánea del fármaco que se administrará puede producir irritación local en el lugar de inyección, pero no se han observado otros efectos relacionados con la vía de administración. Debe saber que el tratamiento con metotrexato puede producir efectos secundarios, que se describen a continuación de acuerdo a su frecuencia de aparición:

Muy frecuentes (≥1/10): pérdida del apetito, náuseas, vómitos, dolor abdominal, úlceras orales y en garganta, alteración de la función del hígado (alteración del perfil hepático en análisis sanguíneo).

Frecuentes (≥1/100, <1/10): disminución en el número de glóbulos blancos (leucopenia) y plaquetas (trombocitopenia), anemia, dolor de cabeza, fatiga y somnolencia, neumonitis intersticial aguda, diarrea y lesiones cutáneas (exantema, eritema, prurito).

Poco frecuentes (≥1/1.000, <1/100): disminución del número de células sanguíneas (pancitopenia) y otros trastornos hematológicos. Vértigo, confusión, depresión, convulsiones. Fibrosis pulmonar. Úlceras gastrointestinales y enfermedades del hígado, como la cirrosis. Pueden aparecer lesiones cutáneas graves (urticaria, fotosensibilidad, pérdida de cabello, herpes zóster, vasculitis, síndrome de Steven-Johnson). Dolor muscular y articular, osteoporosis. Ulceración vaginal y de la vejiga. Reacciones alérgicas severas. Se han descrito casos individuales de linfoma (tumor hematológico) posiblemente asociados a metotrexato.

Raros (≥1/10.000, <1/1.000): faringitis, asma. Inflamación intestinal y malabsorción, gingivitis, hepatitis aguda. Lesiones cutáneas (pigmentación de las uñas, acné, rash petequial, eritema multiforme). Fracturas óseas y fallo renal.

Muy raros (<1/10.000): sepsis e infecciones oportunistas graves, que podrían originar la muerte. Trastornos hematológicos severos (depresión medular, anemia aplásica, trastornos linfoproliferativos, inmunosupresión), insomnio, cansancio, astenia, dolor, sabor metálico. Meningismo y meningitis. Trastornos oculares (conjuntivitis, retinopatía). Alteraciones pulmonares (neumonía grave, enfermedad pulmonar obstructiva crónica). Megacolon tóxico, reactivación de la hepatitis crónica y fallo hepático. Trastornos cutáneos (forunculosis, vasculitis alérgica entre otros), disminución de la libido, impotencia, infertilidad y trastornos menstruales.

Debe saber que en caso de recibir terapia con metotrexato, estará recibiendo también un suplemento oral de ácido fólico destinado a disminuir la aparición de algunos efectos adversos derivados del uso de metotrexato. Esta práctica está recomendada de forma habitual en el uso de metotrexato fuera de este estudio.

Fertilidad, embarazo y lactancia

Metotrexato está totalmente contraindicado durante el embarazo. Es tóxico sobre la reproducción, sobre todo en el primer trimestre. Es teratógeno y produce anomalías congénitas y/o muerte fetal. Las mujeres en edad fértil deben realizarse una prueba de embarazo para excluir que estén embarazadas antes de comenzar el tratamiento. Durante el uso de metotrexato, las mujeres no deben quedarse embarazadas y los pacientes, tanto hombres como mujeres, en edad reproductiva, deben utilizar métodos anticonceptivos eficaces durante el tratamiento y al menos en los 6 meses posteriores. Asimismo, este medicamento se excreta en la leche materna y puede causar toxicidad en el lactante, de forma que también está contraindicado su uso durante la lactancia.

TRATAMIENTOS ALTERNATIVOS

En los pacientes que se encuentran en su situación clínica, esto es, que padecen enfermedad de Crohn y acaban de someterse a una resección intestinal por primera vez, que no son fumadores activos y cuya enfermedad tiene un comportamiento inflamatorio o estenosante, actualmente existen dos maneras de abordar el manejo. Por un lado puede no tratarse y si en la endoscopia de control que se realiza a los seis meses de la cirugía hay lesiones intestinales, comenzar un tratamiento. Por otro lado, puede comenzar a tratarse tras la cirugía para prevenir que aparezcan esas lesiones. En este caso, pueden utilizarse fármacos como la mesalazina, el metronidazol o la azatioprina. Ambos manejos son igualmente válidos en la actualidad.

SEGURO

Estará cubierto por una póliza de responsabilidad civil contratada por el promotor del estudio que cubre cualquier posible daño y perjuicio que pueda derivarse de la participación en el estudio, tal y como lo exige la legislación española vigente.

CONFIDENCIALIDAD

El tratamiento, la comunicación y la cesión de los datos de carácter personal de todos los participantes del estudio se ajustará a la Ley Orgánica 15/1999, de 13 de diciembre de protección de Datos de Carácter Personal. De acuerdo a esta ley, usted tiene derecho al acceso, modificación, oposición y cancelación de sus datos y para ello podrá dirigirse a su médico en el estudio. Los datos que se recogerán en este estudio se identificarán mediante un código y tan sólo su doctor y

colaboradores podrán identificar posteriormente a los participantes. En ningún caso se transmitirán datos a terceros que contengan información que pueda identificarle directamente, como nombre y apellidos, dirección u otros.

El acceso a su información personal queda restringido a los investigadores de este estudio, autoridades sanitarias (AEMPS), CEIC y personal autorizado por el promotor del estudio, cuando se precise para comprobar los datos y procedimientos del estudio, pero siempre manteniendo la confidencialidad de acuerdo a la legislación vigente.

Si decide retirar su consentimiento a participar en este estudio, ningún dato se añadirá a la base de datos y puede exigir la destrucción de cualquier dato o muestra previamente registrados.

COMPENSACIÓN ECONÓMICA

El promotor del estudio es el responsable de la gestión y de la financiación del mismo. Usted no tendrá que pagar por los medicamentos del estudio.

CONTACTO CON EL INVESTIGADOR

Para cualquier duda o información adicional sobre el estudio o sobre sus derechos como participante en un ensayo clínico, deberá contactar con el investigador de su hospital.

Datos de contacto: _____

FORMULARIO DE CONSENTIMIENTO INFORMADO DEL PACIENTE

Nombre y apellidos del paciente:

Fecha de nacimiento:

1. Confirmo que mi médico, el Dr./la Dra. _____ (nombre y apellidos del médico) me han informado de forma comprensible para mí y con detalle sobre los objetivos y el significado de este estudio y me ha proporcionado una HOJA DE INFORMACIÓN AL PACIENTE.

2. He entendido que el médico responsable del estudio es el Dr./Dra. _____ y es a quién debo referirme en caso de tener algún problema.

3. He entendido la información, tanto oral como escrita, que me han proporcionado*. He tenido tiempo para reflexionar sobre qué significa el estudio para mí y he consultado todas las dudas que hayan podido surgirme con respecto a los detalles del estudio.

4. Entiendo que mi participación en este estudio es totalmente voluntaria y que puedo retirarme del mismo en cualquier momento y por cualquier motivo, sin tener que dar explicaciones, y sin que esto repercuta en ningún caso en mi atención o mis cuidados médicos.

5. Doy mi autorización para que mis datos clínicos obtenidos en este estudio, sean procesados junto con mis iniciales, fecha de nacimiento y sexo, y que estos datos podrán ser conservados y procesados electrónicamente para su evaluación científica.

6. Doy mi aprobación para que las Autoridades Sanitarias correspondientes tengan acceso a mi historia clínica para comprobar si el estudio ha sido llevado a cabo según las leyes y requisitos vigentes.

7. Declaro que presto voluntariamente mi conformidad para participar en este estudio mediante el presente documento.

**Si el paciente no puede leer o firmar, deberán estar presentes 2 testigos imparciales durante la discusión del consentimiento informado*

A firmar y fechar por el paciente.

Nombre: Firma:

Fecha:

Declaración del Investigador del Consentimiento Informado del paciente:

Yo, _____ he explicado en su totalidad los detalles de este estudio, tal y como se describe en la hoja de información al paciente:

Fecha: Firma:

**Declaración de los testigos del Consentimiento informado del paciente:*

Al firmar este documento, atestiguamos que la información fue explicada con claridad y entendida por el paciente, y que el paciente otorgó libremente su consentimiento informado.

Nombre de los testigos:

Fecha: Firma:

Fecha: Firma:

FULL D'INFORMACIÓ AL PACIENT

Títol de l'estudi:

Eficàcia del tractament amb metotrexat per a la prevenció de la recurrència postquirúrgica de la malaltia de Crohn

Assaig clínic multicèntric, a doble cec i controlat amb placebo sobre l'eficàcia d'utilitzar metotrexat com a tractament preventiu de la recurrència postquirúrgica a la malaltia de Crohn.

Codi del promotor:

Promotor:

Investigadors principals:

Centre:

Ens dirigim a vostè per a informar-li sobre l'estudi d'investigació a què és convidat a participar. Aquest estudi ha estat aprovat pel Comitè Ètic d'Investigació Clínica (CEIC) d'aquest hospital i l'*Agencia Española del Medicamento y Productos Sanitarios* (AEMPS), d'acord a la legislació vigent, el Reial Decret 223/2004, de 6 de Febrer, pel que es regulen els assajos clínics amb medicaments.

Abans que decideixi sobre la seva participació a l'estudi, és important que rebi i comprengui correctament la informació continguda en aquest document. Per això, és necessari que llegeixi amb temps i detingudament la següent informació, que podrà consultar amb les persones que cregui adients. El seu metge li aclarirà qualsevol dubte que li pugui sorgir després de l'explicació.

CONDICIONS DE PARTICIPACIÓ

La seva participació en aquest estudi és totalment voluntària i pot decidir no participar o retirar-se d'aquest en qualsevol moment, sense donar-ne cap explicació. La decisió de no participar en aquest estudi o de retirar-se un cop s'hagi inclòs mai afectarà als seus drets legals i ètics a rebre tractament: vostè continuarà rebent el tractament més adequat per a la seva malaltia.

Tanmateix, si decideix retirar-se d'aquest estudi és important que n'informi el seu metge. D'igual manera, el seu metge podria decidir retirar-lo de l'estudi en cas de no complir amb el protocol que s'estableix o si experimenta algun efecte secundari important.

DESCRIPCIÓ DE L'ESTUDI

Objectius de l'estudi

Se li ha ofert participar en aquest estudi perquè pateix malaltia de Crohn i acaba de ser sotmès a una resecció intestinal. Amb molta freqüència, reapareix la malaltia, el que coneixem com a recurrència postquirúrgica.

Aquest estudi té per objectiu valorar l'eficàcia (prevenció de la recurrència postquirúrgica tant endoscòpica com simptomàtica) i el perfil de seguretat (efectes secundaris) de fer servir metotrexat en la prevenció de la recurrència de la malaltia.

Procediments de l'estudi

Es preveu la participació de 132 pacients en aquest estudi, distribuïts en diferents hospitals a Espanya. Hi haurà dos grups d'intervenció i cadascú constarà de 66 pacients.

Aquest estudi farà servir dues pautes de tractament, i vostè rebrà, de forma aleatòria, una de les dues. Ni vostè ni els investigadors que l'atenguin coneixeran a quin dels grups ha estat assignat:

- Metotrexat administrat via subcutània a dosis de 25mg, un cop per setmana, durant 24 setmanes amb un suplement setmanal de 5mg d'àcid fòlic via oral, un cop per setmana.
- Placebo (substància sense principi actiu farmacològic) d'administració subcutània, un cop per setmana, durant 24 setmanes juntament amb un altre placebo oral un cop per setmana. Ambdós placebos seran idèntics en aparença, dosi i forma d'administració que els fàrmacs corresponents administrats a l'altre grup de tractament.

Metotrexat està comercialitzat a Espanya i s'utilitza en el tractament de malalties inflamatòries, com l'artritis reumatoide, des de fa molts d'anys. Metotrexat s'utilitza a la pràctica clínica habitual com a medicament immunosupressor de segona línia en pacients que no responen o no toleren altres fàrmacs, com l'azatioprina i la mercaptopurina, en la inducció i el manteniment de la remissió de la malaltia de Crohn. Tanmateix, aquest fàrmac no té autoritzada la indicació per a la malaltia de Crohn i es fa servir en el que es coneix com a "us compassiu", és a dir, es fa servir tot i no tenir l'autorització en aquesta malaltia perquè es coneix que pot ésser beneficiós per al pacient.

Ha de conèixer que, tot i que ja s'han realitzat estudis que provaren l'eficàcia del metotrexat en pacients amb malaltia de Crohn, aquest és el primer assaig clínic que avalua la seva eficàcia per a la prevenció de la recurrència postquirúrgica de la malaltia.

Què haurà de fer si decideix participar en aquest estudi?

Un cop iniciat el tractament, vostè seguirà una sèrie de controls per a garantir un desenvolupament correcte i segur de l'estudi. Alguns d'aquests controls, com ara la realització d'anàlisis sanguínies o visites mèdiques, es farien igualment en el seu cas, encara que no participés en aquest estudi, per al control de la evolució de la malaltia després de la cirurgia, i més periòdicament en el cas que rebés alguna altra medicació per a la prevenció de la recurrència postquirúrgica. De forma addicional, serà visitat pel seu metge i se li practicaran anàlisis de sang destinats a avaluar la seguretat del medicament que estarà rebent. També rebrà instruccions sobre com ha d'administrar el fàrmac en una consulta amb infermeria. A les 24 setmanes del tractament (aproximadament als 6 mesos) se li realitzarà un estudi endoscòpic (colonoscòpia amb ileoscòpia), per a avaluar la seva evolució. Aquesta prova forma part també de la pràctica clínica habitual fora d'aquest estudi.

Ha de conèixer que metotrexat s'administra per via subcutània per assegurar que el fàrmac actua adequadament. Haurà de complir amb el tractament, administrat com li indicarà específicament un/a infermer/a, Durant l'estudi no podrà prendre certs medicaments. En cas de ser necessari, el seu metge li indicarà quins podria prendre. Vostè haurà de notificar qualsevol altre tractament que estigui prenent així com la possible aparició d'efectes secundaris al seu metge.

Totes les persones que participin en aquest estudi, tant homes com dones, hauran de fer servir mètodes anticonceptius adequats des de l'inici del tractament i per un total de 12 mesos. Metotrexat està contraindicat en l'embaràs i lactància, per la toxicitat que podria produir.

Beneficis derivats de la seva participació a l'estudi

Vostè podria beneficiar-se fora d'aquest estudi, tant de tractament preventiu de forma immediata a la cirurgia com de rebre'l només si apareixen lesions en l'endoscòpia de control als 6 mesos segons la pràctica clínica actual. Vostè podria beneficiar-se del tractament de l'estudi però també és possible que no n'obtingui cap benefici. A més a més, amb la seva participació vostè està contribuït a millorar el coneixement sobre el maneig terapèutic d'aquest problema.

Riscos derivats de la seva participació a l'estudi

Ha de conèixer que l'administració subcutània del fàrmac que s'administrarà pot produir irritació local en el lloc d'injecció, però no s'han observat altres efectes relacionats amb la via d'administració. Ha de saber que el tractament amb metotrexat pot produir efectes secundaris, que es descriuen a continuació d'acord amb la seva freqüència d'aparició:

Molt freqüents (≥1/10): pèrdua de la gana, nàusees, vòmits, dolor abdominal, úlceres orals i de la gola, alteració de la funció del fetge (alteració del perfil hepàtic en anàlisi de sang).

Freqüents (≥1/100, <1/10): disminució en el número de glòbuls blancs (leucopènia), i plaquetes (trombocitopènia), anèmia, mal de cap, fatiga, somnolència, pneumonitis intersticial aguda, diarrea, lesions cutànies (exantema, eritema, prurit).

Poc freqüents (≥1/1.000, <1/100): disminució del número de cèl·lules sanguínies (pancitopènia) i altres trastorns hematològics. Vertigen, confusió, depressió, convulsions. Fibrosi pulmonar. Úlceres gastrointestinals i malalties del fetge, com la cirrosi. Poden aparèixer lesions cutànies greus (urticària, fotosensibilitat, pèrdua de cabell, herpes zòster, vasculitis, síndrome de Steven-Johnson). Dolor muscular i articular, osteoporosi. Ulceració vaginal i de la bufeta urinària. Reaccions al·lèrgiques greus. S'han descrit casos individuals de limfoma (tumor hematològic) possiblement associat a metotrexat.

Rars (≥1/10.000, <1/1.000): faringitis, asma. Inflamació intestinal i malabsorció, gingivitis, hepatitis aguda. Lesions cutànies (pigmentació de les ungles, acne, rash petequial, eritema multiforme). Fractures òssies i fracàs renal.

Molt rars (<1/10.000): sèpsis i infeccions oportunistes greus, que podrien originar la mort. Trastorns hematològics severs (depressió medul·lar, anèmia aplàsica, trastorns limfoproliferatius,

immunosupressió). Insomni, cansament, astènia, dolor, gust metàl·lic. Meningisme i meningitis. Trastorns oculars (conjuntivitis, retinopatia). Alteracions pulmonars (pneumònia greu, malaltia pulmonar obstructiva crònica). Megacolon tòxic, reactivació de l'hepatits crònica i fracàs hepàtic. Trastorns cutanis (furunculosi, vasculitis al·lèrgica entre d'altres), disminució de la libido, impotència, infertilitat i trastorns menstruals.

Ha de saber que en cas de rebre teràpia amb metotrexat, estarà rebent també un suplement oral d'àcid fòlic destinat a disminuir l'aparició d'alguns efectes adversos derivats de l'ús del metotrexat. Aquesta pràctica està recomanada de manera habitual en l'ús del metotrexat fora d'aquest estudi.

Fertilitat, embaràs i lactància

Metotrexat està totalment contraindicat durant l'embaràs. És tòxic sobre la reproducció, sobretot en el primer trimestre. És teratogen i produeix anomalies congènites i/o mort fetal. Les dones en edat fèrtil han de realitzar-se una prova d'embaràs per a excloure que estiguin embarassades abans de començar el tractament. Durant l'ús del metotrexat, les dones no han de quedar embarassades i els pacients, tant homes com dones, en edat reproductiva, han de fer servir mètodes anticonceptius eficaços durant el tractament i al menys en els 6 mesos posteriors. Així mateix, aquest medicament s'excreta a la llet materna i pot causar toxicitat en el lactant, de manera que també està contraindicat durant la lactància.

TRACTAMENTS ALTERNATIUS

Als pacients que es troben a la seva situació clínica, és a dir, que pateixen malaltia de Crohn i acaben de ser sotmesos a una resecció intestinal per primera vegada, que no són fumadors actius i amb un comportament inflamatori o estenosant de la seva malaltia, actualment existeixen dues maneres d'abordar-ne el maneig. D'una banda, podria no tractar-se i si a l'endoscòpia de control realitzada als sis mesos de la cirurgia hi ha lesions intestinals, començar un tractament. De l'altra, podria començar un tractament després de la cirurgia per a prevenir que apareguin aquestes lesions. En aquest cas, poden fer-se servir fàrmacs com la mesalazina, el metronidazol o l'azatioprina. Ambdós manejos són igualment vàlids en el moment actual.

ASSEGURANÇA

Estarà cobert per una pòlissa de responsabilitat civil contractada pel promotor de l'estudi que cobreix qualsevol dany i perjudici que pogués derivar-se'n de la participació a l'estudi, tal com exigeix la legislació espanyola vigent.

CONFIDENCIALITAT

El tractament, la comunicació i cessió de les dades de caràcter personal de tots els participants de l'estudi s'ajustarà a la Llei Orgànica 15/1999, de 13 de Desembre, de Protecció de Dades de Caràcter Personal. D'acord amb aquesta llei, vostè té dret al accés, modificació, oposició i cancel·lació de les seves dades i per a això podrà dirigir-se al seu metge en l'estudi. Les dades que es recolliran en aquest estudi s'identificaran mitjançant un codi i només els investigadors i col·laboradors d'aquest estudi podran identificar posteriorment als participants. En cap cas es

transmetran dades a tercers que continguin informació que pugui identificar-lo directament, com nom i cognoms, direcció o d'altres.

L'accés a la seva informació personal queda restringit als investigadors, autoritats sanitàries (AEMPS), CEIC i personal autoritzat pel promotor de l'estudi, quan es precisi per a comprovar les dades i procediments del mateix, però sempre mantenint-ne la confidencialitat d'acord amb la legislació vigent.

Si decideix retirar el seu consentiment a participar en aquest estudi, cap dada s'afegirà a la base de dades i podrà exigir la destrucció de qualsevol dada o mostra prèviament enregistrada.

COMPENSACIÓ ECONÒMICA

El promotor de l'estudi és el responsable de la gestió del finançament del mateix. Vostè no haurà de pagar pels medicaments de l'estudi.

CONTACTE AMB L'INVESTIGADOR

Per a qualsevol dubte o informació addicional sobre l'estudi o sobre els seus drets com a participant a un assaig clínic, haurà de contactar amb l'investigador del seu hospital.

Dades de contacte:_____

FORMULARI DE CONSENTIMENT INFORMAT DEL PACIENT

Nom i cognoms del pacient:

Data de naixement:

1. Confirmo que el meu metge, el Dr./la Dra. _____ (nom i cognoms del metge) m'han informat de forma comprensible per a mi i amb detall sobre els objectius i el significat d'aquest estudi i m'han proporcionat un FULL D'INFORMACIÓ AL PACIENT.

2. He entès que el metge responsable de l'estudi és el Dr./Dra. _____ i és a qui he d'adreçar-me en cas de tenir algun problema.

3. He entès la informació, tant oral com escrita, que m'han proporcionat*. He tingut temps per a reflexionar sobre què significa l'estudi per a mi i he consultat tots els dubtes que m'han sorgit respecte als detalls de l'estudi.

4. Entenc que la meva participació en aquest estudi és totalment voluntària i que puc retirar-me del mateix en qualsevol moment i per qualsevol raó, sense haver-ne de donar explicacions, i sense que això repercuteixi en cap cas en la meva atenció o cures mèdiques.

5. Dono la meva autorització a què les meves dades clíniques obtingudes en aquest estudi, siguin processades juntament amb les meves inicials, data de naixement i sexe, i que aquestes dades podran ser conservades i processades electrònicament per a la seva avaluació científica.

6. Dono la meva aprovació per a que les Autoritats Sanitàries corresponents tinguin accés a la meva història clínica per comprovar si l'estudi s'ha dut a terme segons les lleis i els requisits vigents.

7. Declaro que dono voluntàriament la meva conformitat per a participar en aquest estudi mitjançant el present document.

**Si el pacient no pot llegir o firmar, hauran de ser presents 2 testimonis imparcials durant la discussió del consentiment informat.*

A signar i datar pel pacient: Nom: Signatura: Data:
Declaració de l'investigador del Consentiment Informat del pacient: Jo, _____ he explicat en la seva totalitat els detalls d'aquest estudi, tal com es descriu al full d'informació al pacient: Data: Signatura:
**Declaració dels testimonis del Consentiment Informat del pacient::* En signar aquest document, testifiquem que la informació va ser explicada amb claredat i entesa pel pacient, i que el pacient va atorgar lliurement el seu consentiment informat: Nom dels testimonis: Data: Signatura: Data: Signatura: