
RemRegister

A study in the real-world practice to evaluate the impact of biosimilar infliximab (**Rem**sima) in clinical outcomes in patients with inflammatory bowel diseases: a 2-year longitudinal analysis from the GEDII **Reg**istry

Study sponsor: Grupo de Estudo da Doença Inflamatória Intestinal (GEDII)

Name of Scientific Coordinator: Prof. Fernando Magro

Primary Objectives

- To evaluate the impact of Remsima in inducing clinical response among biologic-naïve patients with IBDs registered in the GEDII Registry followed for two years.

- To evaluate the impact of Remsima in inducing clinical remission among biologic-naïve patients with IBDs registered in the GEDII Registry followed for two years.

- To evaluate the impact of Remsima in promoting mucosal healing, among biologic-naïve patients registered in the GEDII Registry followed for two years.

- To evaluate the impact of Remsima in promoting biomarkers remission by normalization of calprotectin.

Secondary Objectives

- To evaluate the impact of Remsima in maintaining clinical remission among patients with IBDs registered in the GEDII Registry who switched from Remicade to Remsima, followed for two years.
- To evaluate the impact of Remsima in maintaining endoscopic remission among patients with IBDs registered in the GEDII Registry who switched from Remicade to Remsima, followed for two years.
- To evaluate the impact of Remsima in maintaining steroid-free remissions among patients with IBDs registered in the GEDII Registry who switched from Remicade to Remsima, followed for two years.
- To evaluate the impact of Remsima in maintaining steroid-free remissions among biologic-naïve patients with IBDs registered in the GEDII Registry, followed for two years.
- To evaluate the rate of Remsima persistence among patients with IBDs registered in the GEDII Registry after two years of follow up.
- To evaluate the impact of Remsima in perianal manifestations measured by the Perianal Disease Activity Index (PDAI), among patients with perianal Chron's disease registered in the GEDII Registry, followed for two years.
- To evaluate the immunogenicity of Remsima among patients registered in the GEDII Registry throughout the 2-year follow up.

Secondary Objectives (cont.)

- To assess serum Remsima levels among patients registered in the GEDII Registry throughout the 2-year follow up.
- To assess the safety profile of Remsima among patients registered in the GEDII Registry throughout the 2-year follow up.
- To explore the correlation between fecal calprotectin levels with mucosal healing and clinical activity among patients with IBDs registered in the GEDII Registry treated with Remsima.
- To explore the correlation of fecal calprotectin levels with serum infliximab levels throughout the 2-year follow up.
- To explore the correlation of fecal calprotectin levels with the development of anti-drug antibodies throughout the 2-year follow up.
- To evaluate the use of health resources among patients with IBDs registered in the GEDII Registry treated with Remsima.

Inclusion Criteria

1. Male or female patients, 18 years or older.

2. Patients with IBD who are registered in the GEDII Registry, including:
   - ❖ Patients with moderate to severe, active Crohn's disease who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies.
   - ❖ Patients with fistulising active Crohn's disease who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy).
   - ❖ Patients with moderate to severe active ulcerative colitis who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

3. Patients who initiated Remsima according to physician's criteria, including:
   - ❖ Anti-TNF-alfa-naïve patients.
   - ❖ Patients on treatment with Remicade with stable clinical response (defined as Harvey-Bradshaw Index <5 – for CD patients; or Mayo score < 2 – for UC patients) and who switched to Remsima.

4. Patients already under maintenance treatment with Remsima at time of inclusion in the study.

5. Remsima managed according to local SMPc.

6. Patients who gave their consent to be included in the GEDII Registry.

Exclusion Criteria

1. Patients who are not eligible for anti-TNF-alfa therapy

2. Patients who are being treated with any investigational agent

3. Patients who are not willing to comply with routine clinical appointments

Primary Endpoints

1. **In the subset of biologic-naïve patients with active, moderate to severe CD:**

   - To determine the proportion of patients who had clinical response (3-point reduction in the Harvey-Bradshaw Index) at week 14 after induction therapy with Remsima.

   - To determine the proportion of patients with clinical remission (Harvey-Bradshaw Index < or = 4 points) during maintenance therapy with Remsima at each data collection time points (weeks 14, 22, 30, 38, 46, 54, 62, 70, 78, 86, 94 and 102).

   - To determine the proportion of patients with mucosal healing (defined as absence of mucosal ulceration) during maintenance therapy with Remsima at weeks 54 and 102.

   - To determine the proportion of patients with biomarker remission, defined by calprotectine < 100 µg/g at weeks 2, 6, 14, 22, 38, 54, 70, 86 and 102.

Primary Endpoints (cont.)

2. In the subset of biologic-naïve patients with active, moderate to severe fistulising CD:

- To determine the proportion of patients who had clinical response (defined as a reduction of at least 50 percent in the number of draining fistulas present at baseline, confirmed at two or more consecutive study visits (a minimum of 21 days between consecutive visits is required), after induction therapy with Remsima.

- To determine the rate of loss of response during maintenance therapy with Remsima at each data collection time points (weeks 14, 22, 30, 38, 46, 54, 62, 70, 78, 86, 94 and 102).

- To determine the median time to loss of response during maintenance therapy with Remsima.
  Loss of response is defined as one of the following:
  a) recrudescence of draining fistulas
  b) the need for a change in medication for CD or the need for additional therapy for persistent or worsening luminal disease activity
  c) the need for a surgical procedure for CD for anal disease
  d) discontinuation of the study medication owing to a perceived lack of efficacy

Primary Endpoints (cont.)

3. In the subset of biologic-naïve patients with active, moderate to severe UC:

- To determine the proportion of patients who had clinical response (defined as a 3-point reduction in Partial Mayo score at week 14, after induction therapy with Remsima.
  Partial Mayo Score: Mayo score excluding the endoscopy subscore (range: 0-9).

- To determine the proportion of patients with clinical remission (defined as Partial Mayo score ≤ 2 with no individual subscore >1) at week 14, after induction therapy with Remsima.

- To determine the proportion of patients with mucosal healing (defined as Mayo endoscopy subscore ≤ 1) at week 14, after induction therapy with Remsima.

- To determine the proportion of patients with clinical remission (defined as Partial Mayo score ≤ 2 with no individual subscore >1) during maintenance therapy with Remsima at each data collection time points (weeks 14, 22, 38, 54, 70, 86 and 102).

- To determine the rate of mucosal healing (defined as Mayo endoscopy subscore ≤ 1) during maintenance therapy with Remsima at weeks 54 and 102.

- To determine the proportion of patients with biomarker remission, defined by calprotectine < 100 µg/g at weeks 2, 6, 14, 22, 38, 54, 70, 86, and 102.

Secondary Endpoints

1. **In the subset of patients with CD who switched from Remicade to Remsima**

   - To determine the proportion of patients with clinical remission (defined as Harvey-Bradshaw Index < or =4 points) at each data collection time points up to week 102.

2. **In the subset of patients with fistulising CD who switched from Remicade to Remsima**

   - To determine the rate of loss of response during maintenance therapy with Remsima at each data collection time points up to week 102.

   - To determine the median time to loss of response during maintenance therapy with Remsima.

   - Loss of response is defined as one of the following:
     a) recrudescence of draining fistulas
     b) the need for a change in medication for CD or the need for additional therapy for persistent or worsening luminal disease activity
     c) the need for a surgical procedure for CD for anal disease
     d) discontinuation of the study medication owing to a perceived lack of efficacy

Secondary Endpoints (cont.)

3. In the subset of patients with UC who switched from Remicade to Remsima

- To determine the proportion of patients with clinical remission (defined as Partial Mayo score ≤ 2 with no individual subscore >1) during therapy with Remsima at each data collection time points.

- To determine the rate of mucosal healing (Mayo with endoscopy subscore ≤ 1) during therapy with Remsima at weeks 16, 56 and 96. The proportions found at each time point will be compared with the proportion found at baseline (time of Remsima initiation).

4. In the subset of biologic-naïve patients with perianal CD

- To assess the change in PDAI score at weeks 2, 6, 14, 22, 54 and 102 comparing to baseline score.

The PDAI is based on five variables (the presence or absence of discharge, pain or restriction of activities of daily living, restriction of sexual activity, the type of perianal disease, and the degree of induration. Overall score ranges from 0 to 20, with higher scores indicating more severe disease.

Secondary Endpoints (cont.)

For all the above subsets:

- To determine the proportion of patients who withdrew Remsima during the two year follow up, and reason for discontinuation (persistence on Remsima).
- To determine the rates of steroid-free status and steroid-free remission at week 30, week 54 and week 102 - subset of patients taking corticosteroids at baseline).
- To determine the incidence of adverse events (serious and non-serious) throughout the observation period, including AEs of special interest. AEs of interest include, among others: infusion-related reactions, opportunistic infections, laboratory abnormal values.
- To evaluate the development of anti-drug antibodies (+ or -) at each data collection time points (baseline, weeks 2, 6, 14, 22, 30, 38, 46, 54, 62, 70, 78, 86, 94, 102).
- To determine serum infliximab levels at each data collection time points (baseline, weeks 2, 6, 14, 22, 30, 38, 46, 54, 62, 70, 78, 86, 94, 102).
- To correlate fecal calprotectin levels with mucosal healing (defined as Mayo endoscopy subscore ≤ 1) at each data collection time points among patients with UC.

Secondary Endpoints (cont.)

For all the above subsets (cont.):

- To correlate fecal calprotectin levels with Harvey-Bradshaw Index score at each data collection time points among patients with CD.
- Fecal calprotectin levels and serum infliximab levels at each data collection time points.
- Fecal calprotectin levels and presence of anti-drug antibodies (+ or -) at each data collection time points.
- To describe the use of health resources:
  - IBD-related hospitalizations (number of hospitalizations, and length of stay)
  - Type of surgery
  - Emergency room admissions (number of admissions)
  - Treatments (dose and duration of treatment)
  - Physician consultations (number of consultations and specialty)
  - Exams (type and number of exams).

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CHRONOGRAM A (applicable for CD or fistulising CD patients)

	Infliximab															
	Induction period*			Maintenance period - data collection time points (24-month follow up)												
Information to be collected	**Day1 or basal**	**W2**	**W6**	**W14**	**W22**	**W30**	**W38**	**W46**	**W54**	**W62**	**W70**	**W78**	**W86**	**W94**	**W102**	**Or completion of Fup[3]**
Date of birth	X[4]															
Sex	X[4]															
Height	X[4]															
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BMI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Smoking status	X[4]															
Medical history	X[4]															
Comorbidities	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Disease presentation	X[4]															
Diagnosis CD, location, steroid behavior, prognostic classification.	X[4]															
Clinical activity (HBI)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Nr of draining fistulaes (fistulizing CD)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PDAI (perianal CD)	X	X	X	X	X		X		X		X		X		X	X
Dose of Remsima administered	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Endoscopy	X								X						X	X
Concomitant therapies	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Routine laboratory parameters	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum infliximab levels[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anti-drug antibodies[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fecal sample (calprotectin levels)[2]	X	X	X	X	X		X		X		X		X		X	X
Adverse reactions	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Use of health resources	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

* Data related with induction period **will only be collected** for biologic-naïve patients starting Remsima. Data related with maintenance period is applicable both to biologic-naïve patients and patients who switched from Remicade. W = week, HBI = Harvey Bradshaw Index, PDAI, Perianal Disease Activity Index.

[1] Blood sample to be collected prior to each infusion of Remsima at the scheduled appointment. Sample will be analyzed by Central Laboratory.

[2] Stool sample to be collected and sent for Central Laboratory

[3] Patients in maintenance with Remsima at study inclusion will be followed every 8 weeks (or every 6 weeks, if required) until completing the 24-month follow up period;

[4] Basal data to be collected, regardless of the patient's treatment status at study inclusion.

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DA DOENÇA INFLAMATÓRIA INTESTINAL

CHRONOGRAM B (applicable for UC patients)

	Infliximab															
	Induction period*			Maintenance period - data collection time points (24-month follow up)												
Information to be collected	**Day1 or basal**	**W2**	**W6**	**W14**	**W22**	**W30**	**W38**	**W46**	**W54**	**W62**	**W70**	**W78**	**W86**	**W94**	**W102**	**Or completion of Fup[3]**
Date of birth	X[4]															
Sex	X[4]															
Height	X[4]															
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BMI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Smoking status	X[4]															
Medical history	X[4]															
Comorbidities	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Disease presentation	X[4]															
Diagnosis UC, location, steroid behavior, prognostic classif.	X[4]															
Clinical activity (Partial Mayo)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dose of Remsima administered	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Endoscopy	X			X					X						X	X
Concomitant therapies	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Routine laboratory parameters	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum infliximab levels[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anti-drug antibodies[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fecal sample (calprotectin levels)[2]	X	X	X	X	X		X		X		X		X	X	X	X
Adverse reactions	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Use of health resources	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

* Data related with induction period **will only be collected** for biologic-naïve patients starting Remsima. Data related with maintenance period is applicable both to biologic-naïve patients and patients who switched from Remicade.

[1] Blood sample to be collected prior to each infusion of Remsima at the scheduled appointment. Sample will be analyzed by Central Laboratory.

[2] Stool sample to be collected and sent for Central Laboratory

[3] Patients in maintenance with Remsima at study inclusion will be followed every 8 weeks (or every 6 weeks, if required) until completing the 24-month follow up period;

[4] Basal data to be collected, regardless of the patient's treatment status at study inclusion.

W = week.

Protocolo prático de colheita de amostras

A - Protocolo de recolha de amostras para doseamento dos níveis de IFX e anti-IFX no soro

(Basal + todas as visitas e VISITA de descontinuação, caso exista)

- Colher 5 mL de sangue venoso periférico para tubo seco (de bioquímica), EM TODAS AS VISITAS **(Caso haja descontinuação do tratamento colher sangue na visita da descontinuação);**
- Deixar o sangue à temperatura ambiente por 1 hora para retracção do coágulo;
- Centrifugar o sangue a 1500 g (≈3000rpm) durante 10 minutos;
- Separar o soro para 2 criotubos, devidamente etiquetados*;
- Congelar o soro a -20ºC;

As amostras de soro podem ser acumuladas e enviadas quando houver um nº considerável de amostras. O envio destas amostras obriga a transporte refrigerado.

_____

*** Etiquetas** - no criotubo deverá constar uma etiqueta com a seguinte informação: ***Número do site (centro) + código do doente (CRF) + nº da visita + data de colheita. As etiquetas serão enviadas juntamente com os kits de colheita***

B- Protocolo de recolha de amostras para doseamento de Calprotectina fecal

(Basal; na fase de Indução (todas as visitas); na fase de manutenção: visita 14, visita 22, visita 38, visita 54, visita 70, visita 86, visita 102 e Visita de descontinuação, caso exista)

a) Recolha de fezes

Colher, no mínimo, 2 g de amostra fecal com ajuda do EasySampler kit

Levante o assento da sanita e limpe a superfície

Remova a tira que protege a fita adesiva do EasySampler

Cole metade do EasySampler à parte detrás da sanita. Assegure-se que o centro do EasySampler está formar uma espécie de taça e cole a outra metade do EasySampler à parte frontal da sanita

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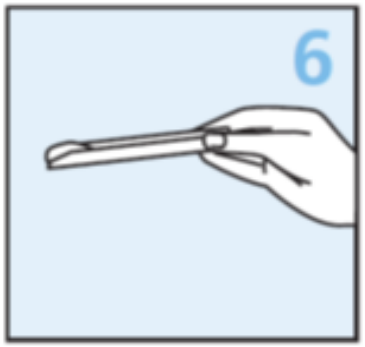
DA DOENÇA INFLAMATÓRIA INTESTINAL

Protocolo prático de colheita de amostras

RemRegister

Baixe o assento da sanita

Defeque



Colha a amostra de fezes

Levante o assento da sanita, descole o EasySampler e puxe o autoclismo, deixando o EasySampler seguir com o fluxo de água

Importante:

Repita a descarga até um fluxo de 10-15 L de água;

Restos de fita adesiva poderão ser removidos com álcool etílico.

b) Armazenamento de amostras de fezes

Para cada doente, a amostra fecal deve ser recolhida, num tubo devidamente identificado*. Será necessário no mínimo 2 g de amostra. As amostras podem ficar armazenadas até ao seu envio, entre 2 a 8ºC, num prazo **máximo de 48 horas após a colheita**.

_____

*** Etiquetas** - no criotubo deverá constar uma etiqueta com a seguinte informação: ***Número do site (centro) + código do doente (CRF) + nº da visita + data de colheita. As etiquetas serão enviadas juntamente com os kits de colheita.***

O centro deverá contactar o GEDII (Dr.ª Sandra Dias, email: gedi@med.up.pt), informando a necessidade do serviço de transporte.

Protocol-Specific Analysis Requisition Form

Study: REMREGISTER

"A study in the real-world practice to evaluate the impact of biosimilar infliximab (Remsima) in clinical outcomes in patients with inflammatory bowel diseases: a 2-year longitudinal analysis from the GEDII registry"

Sponsor: GEDII

Site Nr: __ __ __

Patient ID (CRF Nr) #: __ __ __

Week Nr __ __

Date of Birth (month/year): __ __ / __ __ __ __

Gender at birth: ____

Shipped Samples (tick when applicable)	Description	Collection Date (day/month/year)	Sample ID
	Fecal Calprotectin		
	IFX		

REQUESTER INFORMATION

Name: _____ Date: _____

Signature: _____

ENCLOSE THE ORIGINAL OF THIS FORM WITH THE SAMPLES BEING SHIPPED TO THE CENTRAL LAB. A COPY SHOULD BE LEFT AT SITE.

FOR SAMPLE SHIPMENT PLEASE CONTACT GEDII: gedi@med.up.pt