DIRECT

GEDII
GRUPO DE ESTUDO
DA DOENÇA INFLAMATÓRIA INTESTINAL

Study to investigate the correlation of fecal calprotectin with serum **D**rug levels and development of an ant**I**-d**R**ug antibodi**E**s among adult patients with inflammatory bowel disease re**C**eiving anti-**T**NF-alfa treatment or Vedoluzimab treatment - Direct Study

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

Name of Scientific Coordinator: Prof. Fernando Magro

Primary Objectives

Among biologic-naïve and non-naïve patients with CD or patients with UC registered in the GEDII Registry:

- To explore the association of fecal calprotectin levels with serum adalimumab/golimumab levels throughout a period of 2 years.

- To explore the association of fecal calprotectin levels with the development of anti-adalimumab/anti- golimumab antibodies throughout a period of 2 years.

- To explore the association of fecal calprotectin levels with serum IFX/Vedoluzimab levels throughout a period of 2 years.

- To explore the association of fecal calprotectin levels with the development of anti-IFX/anti-Vedoluzimab antibodies throughout a period of 2 years.

Secondary Objectives

Among biologic-naïve and non-naïve patients with CD or patients with UC registered in the GEDII Registry:

- To explore the association of serum adalimumab/golimumab levels with the development of anti-adalimumab/anti- golimumab antibodies.
- To explore the association of serum adalimumab/golimumab levels with clinical activity throughout a period of 2 years.
- To explore the association of development of anti-adalimumab/anti-golimumab antibodies with clinical activity throughout a period of 2 years.
- To explore the association of serum adalimumab/golimumab levels with patient reported clinical outcome throughout a period of 2 years.
- To explore the association of development of anti-adalimumab/anti-golimumab antibodies with patient reported clinical outcome throughout a period of 2 years.
- To explore the association of therapeutic attitude with serum adalimumab/golimumab levels throughout a period of 2 years.
- To explore the association of therapeutic attitude with the development of anti-adalimumab/anti-golimumab antibodies throughout a period of 2 years.

Secondary Objectives (cont.)

Among biologic-naïve and non-naïve patients with CD or patients with UC registered in the GEDII Registry (cont.):

- To explore the association of serum IFX/Vedoluzimab levels with the development of anti-IFX/anti-Vedoluzimab antibodies.
- To explore the association of serum IFX/Vedoluzimab levels with clinical activity throughout a period of 2 years.
- To explore the association of development of anti-IFX/anti-Vedoluzimab antibodies with clinical activity throughout a period of 2 years.
- To explore the association of serum IFX/Vedoluzimab levels with patient reported clinical outcome throughout a period of 2 years.
- To explore the association of development of anti-IFX/anti-Vedoluzimab antibodies with patient reported clinical outcome throughout a period of 2 years.
- To explore the association of therapeutic attitude with serum IFX/Vedoluzimab levels throughout a period of 2 years.

Secondary Objectives (cont.)

Among biologic-naïve and non-naïve patients with CD or patients with UC registered in the GEDII Registry (cont.):

- To explore the association of therapeutic attitude with development of anti-IFX/anti-Vedoluzimab antibodies throughout a period of 2 years.
- To explore the association of clinical activity with patient reported clinical outcome among patients receiving adalimumab/golimumab throughout a period of 2 years.
- To explore the association of clinical activity with patient reported clinical outcome among patients receiving IFX/Vedoluzimab throughout a period of 2 years.
- To explore the association of calprotectin levels with clinical activity among the subgroup of patients who were co-medicated with azathioprine (AZA).
- To explore the association of calprotectin levels with clinical activity among the subgroup of patients who were co-medicated with methotrexate (MTX).

Inclusion Criteria

1. Male or female patients, 18 years or older

2. Patients who are registered in the GEDII Registry

3. Patients with moderate to severe active Crohn's disease or moderate to severe active Ulcerative Colitis

4. Patients receiving anti-TNF-alfa agents (adalimumab, golimumab, infliximab) or vedoluzimab according to the local approved label, including:

   - Biologic-naïve patients initiating induction with adalimumab, golimumab, infliximab or vedoluzimab at time of inclusion in the study

   - Patients already under maintenance treatment with adalimumab, golimumab, infliximab or vedoluzimab at time of inclusion in the study

5. Patients who gave their informed consent

Exclusion Criteria

1. Patients who are not eligible for therapy with anti-TNF-alfa (adalimumab, golimumab, infliximab) or vedoluzimab

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 and non-naïve patients with active, moderate to severe CD receiving adalimumab:**

    - Fecal calprotectin levels and serum adalimumab levels at each data collection time points.

    - Fecal calprotectin levels and presence of anti-adalimumab antibodies (+ or -) at each data collection time points.

2. **In the subset of biologic-naïve and non-naïve patients with active, moderate to severe CD receiving IFX/Vedoluzimab:**

    - Fecal calprotectin levels and serum IFX/Vedoluzimab levels at each data collection time points.

    - Fecal calprotectin levels and presence of anti-IFX/anti-Vedoluzimab antibodies (+ or -) at each data collection time points.

Primary Endpoints

3. **In the subset of biologic-naïve and non-naïve patients with active, moderate to severe UC receiving adalimumab/golimumab:**

   - Fecal calprotectin levels and serum adalimumab/golimumab levels at each data collection time points.
   - Fecal calprotectin levels and presence of anti-adalimumab/anti-golimumab antibodies (+ or -) at each data collection time points.

4. **In the subset of biologic-naïve and non-naïve patients with active, moderate to severe UC receiving IFX/Vedoluzimab:**

   - Fecal calprotectin levels and serum IFX/Vedoluzimab levels at each data collection time points.
   - Fecal calprotectin levels and presence of anti-IFX/anti-Vedoluzimab antibodies (+ or -) at each data collection time points.

Secondary Endpoints

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

   - Serum adalimumab levels and anti-adalimumab antibodies (+ or -) at each data collection time points.
   - Serum adalimumab levels and clinical activity (HBI) at each data collection time points.
   - Anti-adalimumab antibodies (+ or -) and clinical activity (HBI) at each data collection time points.
   - Serum adalimumab levels and patient-reported clinical activity (Patient reported HBI) at each data collection time points.
   - Anti-adalimumab antibodies (+ or -) and patient-reported clinical activity (Patient reported HBI) at each data collection time points.
   - Therapeutics administered for CD (name and dose) and serum adalimumab levels.
   - Therapeutics administered for CD (name and dose) and anti-adalimumab antibodies (+ or -).

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Secondary Endpoints (cont.)

2. **In the subset of biologic-naïve and non-naïve patients with active, moderate to severe CD receiving IFX/Vedoluzimab:**

   - Serum IFX/Vedoluzimab levels and anti-IFX/anti-Vedoluzimab antibodies (+ or -) at each data collection time points.
   - Serum IFX/Vedoluzimab levels and clinical activity (HBI) at each data collection time points.
   - Anti-IFX/anti-Vedoluzimab antibodies (+ or -) and clinical activity (HBI) at each data collection time points.
   - Serum IFX/Vedoluzimab levels and patient-reported clinical activity (Patient reported HBI) at each data collection time points.
   - Anti-IFX/anti-Vedoluzimab antibodies (+ or -) and patient-reported clinical activity (Patient reported HBI) at each data collection time points.
   - Therapeutics administered for CD (name and dose) and serum IFX/Vedoluzimab levels.
   - Therapeutics administered for CD (name and dose) and anti-IFX/anti-Vedoluzimab antibodies (+ or -).

Secondary Endpoints (cont.)

3. **In the subset of biologic-naïve and non-naïve patients with active, moderate to severe UC receiving adalimumab/golimumab:**

   - Serum adalimumab/golimumab levels and anti-adalimumab/anti-golimumab antibodies (+ or -) at each data collection time points.

   - Serum adalimumab/golimumab levels and clinical activity (partial Mayo Score) at each data collection time points.
     Partial Mayo Score: Mayo score excluding the endoscopy subscore (range: 0-9).

   - Anti-adalimumab/anti-golimumab antibodies (+ or -) and clinical activity (partial Mayo Score) at each data collection time points.

   - Serum adalimumab/golimumab levels and patient-reported clinical activity (Patient reported partial Mayo Score) at each data collection time points.

   - Anti-adalimumab/anti-golimumab antibodies (+ or -) and patient-reported clinical activity (Patient reported partial Mayo Score) at each data collection time points.

   - Therapeutics administered for UC (name and dose) and serum adalimumab/golimumab levels.

   - Therapeutics administered for UC (name and dose) and anti-adalimumab/anti-golimumab antibodies (+ or -)

Secondary Endpoints (cont.)

4. **In the subset of biologic-naïve and non-naïve patients with active, moderate to severe UC receiving IFX/Vedoluzimab:**

   - Serum IFX/Vedoluzimab levels and anti-IFX/anti-Vedoluzimab antibodies (+ or -) at each data collection time points.
   - Serum IFX/Vedoluzimab levels and clinical activity (partial Mayo Score) at each data collection time points.
   - Anti-IFX/anti-Vedoluzimab antibodies (+ or -) and clinical activity (partial Mayo Score) at each data collection time points.
   - Serum IFX/Vedoluzimab levels and patient-reported clinical activity (Patient reported partial Mayo Score) at each data collection time points.
   - Anti-IFX/anti-Vedoluzimab antibodies (+ or -) and patient-reported clinical activity (Patient reported partial Mayo Score) at each data collection time points.
   - Therapeutics administered for UC (name and dose) and serum IFX/Vedoluzimab levels.
   - Therapeutics administered for UC (name and dose) and anti-IFX/anti-Vedoluzimab antibodies (+ or -)

Secondary Endpoints (cont.)

5. **In the subsets of biologic-naïve and non-naïve patients patients with active, moderate to severe CD receiving adalimumab + azathioprine or adalimumab + methotrexate or IFX/Vedoluzimab + azathioprine or IFX/Vedoluzimab + methotrexate:**

   - Fecal calprotectin levels and serum adalimumab/golimumab levels at each data collection time points.
   - Fecal calprotectin levels and presence of anti-adalimumab/anti-golimumab antibodies (+ or -) at each data collection time points.
   - Fecal calprotectin levels and serum IFX/Vedoluzimab levels at each data collection time points.
   - Fecal calprotectin levels and presence of anti-IFX/anti-Vedoluzimab antibodies (+ or -) at each data collection time points.

Secondary Endpoints (cont.)

6. **In the subsets of biologic-naïve and non-naïve patients with active, moderate to severe UC receiving adalimumab/golimumab + azathioprine or adalimumab/golimumab + methotrexate or IFX/Vedoluzimab + azathioprine or IFX/Vedoluzimab + methotrexate:**

   - Fecal calprotectin levels and serum adalimumab/golimumab levels at each data collection time points.
   - Fecal calprotectin levels and presence of anti-adalimumab/anti-golimumab antibodies (+ or -) at each data collection time points.
   - Fecal calprotectin levels and serum IFX/Vedoluzimab levels at each data collection time points.
   - Fecal calprotectin levels and presence of anti-IFX/anti-Vedoluzimab antibodies (+ or -) at each data collection time points.

Secondary Endpoints (cont.)

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

   - Physician's reported HBI and patient-reported HBI (overall and according to anti-TNF-alfa or vedoluzimab).

8. **In the subset of biologic-naïve and non-naïve patients with active, moderate to severe UC:**

   - Physician's reported partial Mayo Score at each data collection time points and patient-reported partial Mayo Score (overall and according to anti-TNF-alfa or vedoluzimab).

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CHRONOGRAM A (CD or UC patients receiving Adalimumab and UC patients receiving Golimumab)

	Adalimumab / Golimumab															
	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 or UC) - location, steroid behavior, prognostic classification.	X[4]															
Clinical activity (HBI / Partial Mayo)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dose of adalimumab/golimumab administered	X	X	X	X	X	X	X	X	X	X	X	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 levels (adalimumab/golimumab)[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anti-drug antibodies (adalimumab/golimumab)[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	X	X	X	X
Patient reported outcomes (HBI or Partial Mayo)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

The data collection time points during maintenance with adalimumab /golimumab are expected every 8 weeks until completing the 24-month follow up period

[1] Blood sample to be collected prior to each infusion of adalimumab at the scheduled appointment (approximately every 12 weeks during maintenance period). Sample will be analyzed by Central Laboratory.

[2] Stool sample to be collected prior to each infusion of adalimumab/golimumab at the scheduled appointment (approximately every 12 weeks during maintenance period). Sample will be analyzed by Central Laboratory.

[3] Patients in maintenance with adalimumab/golimumab at study inclusion will be followed every 12 weeks until completing the 24-month follow up period.

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

W = week. HBI = Harvey Bradshaw Index.

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CHRONOGRAM B (CD or UC patients receiving Infliximab/Vedoluzimab)

	Infliximab / Vedoluzimab															
	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 or UC) - location, steroid behavior, prognostic classification.	X[4]															
Clinical activity (HBI / Partial Mayo)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dose of IFX /Vedo administered	X	X	X	X	X	X	X	X	X	X	X	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 IFX /Vedo levels[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anti-IFX /anti-Vedo 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	X	X	X	X
Patient reported outcomes (HBI or Partial Mayo)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

The data collection time points during maintenance with infliximab/vedoluzimab are expected every 8 weeks (or every 6 weeks, if required) until completing the 24-month follow up period.

[1] Blood sample to be collected prior to each infusion of IFX/Vedo at the scheduled appointment (approximately every 8 weeks).Sample will be analyzed by Central Laboratory.

[2] Stool sample to be collected prior to each infusion of IFX/Vedo at the scheduled appointment (approximately every 8 weeks).Sample will be analyzed by Central Laboratory

[3] Patients in maintenance with infliximab/vedoluzimab at study inclusion will be followed every 8 weeks until completing the 24-month follow up period;

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

W = week; IFX = infliximab, HBI = Harvey Bradshaw Index. Vedo = Vedoluzimab

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Protocolo prático de colheita de amostras

A - Protocolo de recolha de amostras para doseamento dos níveis de fármaco e anti-fármaco 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 de 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***

Protocolo prático de colheita de amostras

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

(Basal + todas as visitas 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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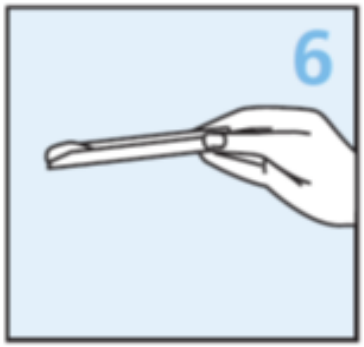
Protocolo prático de colheita de amostras

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**.

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*** 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.

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Protocol-Specific Analysis Requisition Form

Study: DIRECT

"Study to investigate the correlation of fecal calprotectin with serum Drug levels and development of an antI-dRug antibodiEs among adult patients with inflammatory bowel disease reCeiving anti-TNF-alfa treatment or Vedoluzimab treatment - Direct Study"

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		
	Drug: Adalimumab ☐ Golimumab ☐ Infliximab ☐ Vedoluzimab ☐		

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