# International IBD Genetics Consortium

## PRED4

## Thiopurine Induced Liver Injury

## Case Report Form

### Study Code

Please stick study label here

**On completion, please return to:**

IBD Pharmacogenetics Research Office
The Research, Innovation, Learning and Development Centre (RILD)
Barrack Road
Exeter
EX2 5DW

# Thiopurine Induced Liver Injury
## Introduction

Please complete all boxes where indicated and in black ball point pen.

If you make a mistake please put a line through the box, initial and date and write answer to the side.

Complete dates in format dd/mm/yyyy

The patient identification number is the bar code on the front of the CRF. Please transcribe this on to the top of the page in each relevant section.

For study inclusion participants must meet all the major criteria.

# Thiopurine Induced Liver Injury

## Section 1 - Inclusion Criteria

Study code

### 1.1 Major criteria (all must be met)

- ☐ History of inflammatory bowel disease
- ☐ Normal ALT and bilirubin at baseline
- ☐ No pre-existing liver disease
- ☐ Elevation of ALT and/or bilirubin to ≥ 5 times upper limit of normal (defined by local lab)
- ☐ History of thiopurine exposure in the previous 30 days prior to this abnormal blood test
- ☐ Medical opinion implicating thiopurine in development of hepatotoxicity leads to dose reduction or drug withdrawal (even if temporary)

### 1.2 Other risk factor(s) or potential causes for elevated liver enzymes

Drugs: ☐ Yes ☐ No ☐ Unknown

If yes, please specify

Was this drug withdrawn? ☐ Yes ☐ No If yes, date dd/mm/yyyy

Alcohol use: ☐ Yes ☐ No ☐ Unknown

If yes, please provide estimated daily intake

**Tests done to rule out other causes (provide results if done)**

| | |
|---|---|
| Hepatitis A IgM antibody | |
| HbsAg | |
| HCV antibody | |
| Hepatitis E IgM antibody | |
| Anti-smooth muscle antibody or anti-LKM antibody | |
| Immunoglobulin G (IgG) level | |
| Anti-mitochondrial antibody | |
| Serum copper/caeruloplasmin | |
| Haemochromatosis genotyping | |
| Alpha-1 antitrypsisn | |
| Imaging (U/S or MRI showning no biliary dilatation or other biliary abnormality) | |
| Other | |

### 1.3 Participant's eligibility

Is the participant eligible to take part in the clinical trial? ☐ Yes ☐ No

If no, please give reason(s) for screen failure:

| |
|---|
| 1. |
| 2. |
| 3. |

Investigator's name (print) Date dd / mm / yyyy

## Section 2 - Patient Details

Study code

### 2.1 Patient details

Date of Birth dd / mm / yyyy Sex: M F

Weight at time of liver injury (or nearest estimate) kg

Date of weight dd / mm / yyyy Height cm

### 2.2 Ethnicity - *Please tick as appropriate*

**White**

- British
- Irish
- Any other White background

**Black or Black British**

- Caribbean
- African
- Any other Black background

**Mixed**

- White and Black Caribbean
- White and Black African
- White and Asian
- Any other Mixed background

**Chinese or Other Ethnic Group**

- Chinese
- Any other ethnic group (*please specify*)
- Not stated

**Asian or Asian background**

- Indian
- Pakistani
- Bangladeshi
- Any other Asian background

### 2.3 Participant informed consent

Date participant signed written consent form dd / mm / yyyy

Date of blood sample taken dd / mm / yyyy

Name of person taking consent (print)

Designation

## Section 3 - Medical History

**Study code**

### 3.1 Other significant medical history

☐ Yes ☐ No

If yes, please give details here

### 3.2 Smoking history

☐ Never smoked ☐ Ex-smoker ☐ Current smoker

3.2.1 Start date dd / mm / yyyy

3.2.2 End date dd / mm / yyyy

3.2.3 Maximum number of cigarettes per day

## Section 4 - Diagnosis & Classification of IBD

Study code

### 4.1 Diagnosis and classification of IBD

- ☐ Crohn's disease — Date of diagnosis: dd / mm / yyyy
- ☐ Ulcerative Colitis — Date of diagnosis: dd / mm / yyyy
- ☐ IBD unclassified — Date of diagnosis: dd / mm / yyyy

### 4.2 Ulcerative colitis

**4.2.1 The extent of ulcerative colitis can be classified as:**

- ☐ E1 Ulcerative proctitis - inflammation is limited to the rectum (proximal extent of inflammation is distal to the rectosigmoid junction)
- ☐ E2 Left sided UC (distal UC) - inflammation limited to a proportion of the colorectum up to the splenic flexure
- ☐ E3 Extensive UC (pancolitis) - inflammation extends beyond the splenic flexure
- ☐ Ex Unknown

**4.2.2 Disease severity in 2 years prior to development of hepatotoxicity**

- ☐ DS0 Clinical remission. Asymptomatic; no escalation of treatment
- ☐ DS1 Mild relapses – managed with oral or rectal aminosalicylates and/or rectal steroids: **no oral steroids** required
- ☐ DS2 Moderate relapses requiring oral steroids and/or addition of immunomodulator
- ☐ DS3 Severe or refractory disease requiring inpatient admission or colectomy

### 4.3 Crohn's disease

**4.3.1 Location**

- ☐ L1 Ileal
- ☐ L2 Colonic
- ☐ L3 Ileocolonic
- ☐ L4 Isolated upper disease

**4.3.2 Behaviour** - the behaviour can be defined by looking at reports from Barium enema, colonoscopy, MRI, CT

- ☐ B1 Non stricturing, non-penetrating
- ☐ B2 Stricturing
- ☐ B3 Internal penetrating
- ☐ p Perianal disease modifier

## Section 5 - Liver Injury History

Study code

### 5.1 Which thiopurine was suspected of causing liver injury?

☐ Azathioprine ☐ Mercaptopurine

### 5.2 Date thiopurine first commenced

dd / mm / yyyy

### 5.3 Maximum dose of thiopurine in 1 month prior to episode of abnormal LFTs

### 5.3.1 Date when this maximum dose of thiopurine started

dd / mm / yyyy

### 5.4 Presentation

Did the patient present because of:

☐ Routine monitoring ☐ Opportunistic blood test

☐ Symptoms (give details)

☐ Other

### 5.5 Blood test results

| | Date | ALT | Bilirubin | AST | GGT | ALP | Albumin | WCC | Hb | INR | Platelets |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Normal range for your lab | dd/mm/yyyy | | | | | | | | | | |
| Baseline (last blood test before starting thiopurine) | dd/mm/yyyy | | | | | | | | | | |
| First blood test showing elevated ALT/ bilirubin (above reference range for your lab) | dd/mm/yyyy | | | | | | | | | | |
| Blood test showing worst ALT | dd/mm/yyyy | | | | | | | | | | |
| Blood test showing worst bilirubin | dd/mm/yyyy | | | | | | | | | | |
| First recovered ALT (within normal range) | dd/mm/yyyy | | | | | | | | | | |
| First recovered bilirubin (within normal range) | dd/mm/yyyy | | | | | | | | | | |

## Section 5 - Liver Injury History

Study code

### 5.6 Were thiopurine metabolites measured within 2 months of hepatotoxicity?

☐ Yes ☐ No

**If yes**, please give details

Date dd / mm / yyyy 6-TGN 6-MMP

### 5.7 Action taken

☐ Drug withdrawn Date dd / mm / yyyy

☐ Dose decreased Date dd / mm / yyyy

Reduced dose

☐ Tolerated (normal LFTs on this dose) ☐ Not tolerated ☐ Not known

☐ Allopurinol started Date dd / mm / yyyy

Decreased thiopurine dose

☐ Tolerated (normal LFTs on this dose) ☐ Not tolerated ☐ Not known

### 5.8 Was a liver biopsy done?

☐ Yes ☐ No ☐ Unknown

**If yes**, please give results

### 5.9 Did the patient require hospital admission at any stage due to liver toxicity?

☐ Yes ☐ No ☐ Unknown

**If yes**, date of admission dd / mm / yyyy

Date of discharge dd / mm / yyyy

Details

### 5.10 Was the individual ever re-challenged with a thiopurine?

☐ Yes ☐ No ☐ Unknown

**If yes:**

Date of recommencement dd / mm / yyyy

Thiopurine used ☐ Azathiopurine ☐ Mercaptopurine ☐ Not known

Outcome ☐ Tolerated (no adverse reaction)

Dose tolerated

☐ Not tolerated

Adverse reaction

Date drug withdrawn dd / mm / yyyy

## Section 6 - Supplementary Information

Study code

### 6.1 What is the individual's thiopurine methytransferase (TPMT) genotype/ activity ?

Genotype

Activity: ☐ Absent Level (U/ml)

☐ Low (carrier)

☐ Normal

☐ High

Not done: ☐

### 6.2 Has the individual experienced any other adverse effects attributable to azathioprine/mercaptopurine?

☐ Yes ☐ No ☐ Unknown

If yes:

**6.2.1 Leucopaenia (please give lowest WCC with dates)**

**6.2.2 Pancreatitis (please state peak serum amylase/lipase and laboratory reference)**

**6.2.3 Other (please state):**

### 6.3 Other comments

If you have any other comments regarding this patient, please give details here.

# Thiopurine Induced Liver Injury

## Section 7 - Other Drug History

Study code

### 7.1 Other drugs in 3 months prior to developing liver injury

| Drug name | Dose and frequency | Start date | Stop date |
|---|---|---|---|
| | | dd / mm / yyyy | dd / mm / yyyy |
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# Thiopurine Induced Liver Injury

## Section 8 - Principal Investigator Statement  Study code

I have reviewed this CRF and confirm that, to the best of my knowledge, it accurately reflects the study information obtained for this participant. All entries were made either by myself or by a person under my supervision who has signed the Delegation and Signature Log.

Principal Investigator's signature

Date dd / mm / yyyy

Principal Investigator's name (print)

**ONCE SIGNED, NO FURTHER CHANGES CAN BE MADE TO THIS CRF WITHOUT A SIGNED DATA QUERY FORM**