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 ≥ 4 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Was this drug withdrawn?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

Section 5 - Liver Injury History

Study code

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

Please record all ALT/BILIRUBIN results for the re-challenge in the table below regardless of whether it was tolerated or not.

	Date	
Normal range for your lab	dd / mm / yyyy	
Baseline (last ALT test before starting thiopurine)	dd / mm / yyyy	
Baseline (last bilirubin test before the re-challenge)	dd / mm / yyyy	
First blood test showing elevated ALT during the re-challenge (only enter ALT if above reference range for your lab, otherwise leave blank)	dd / mm / yyyy	
First blood test showing elevated bilirubin during the re-challenge (only enter bilirubin if above reference range for your lab, otherwise leave blank)	dd / mm / yyyy	
Blood test showing worst ALT during re-challenge (even if this result is within normal range)	dd / mm / yyyy	
Blood test showing worst bilirubin during re-challenge (even if this result is within normal range)	dd / mm / yyyy	
First recovered ALT (within normal range) after re-challenge	dd / mm / yyyy	
First recovered bilirubin (within normal range) after re-challenge	dd / mm / yyyy	

Please record all drug doses of thiopurine (azathiopurine/6MP) in the concomitant section of the case report form with start and stop dates.

Section 6 - Supplementary Information

Study code

6.1 What is the individual's thiopurine methyltransferase (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.

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
		dd / mm / yyyy	dd / mm / yyyy
		dd / mm / yyyy	dd / mm / yyyy
		dd / mm / yyyy	dd / mm / yyyy
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		dd / mm / yyyy	dd / mm / yyyy

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