An Independent Blinded Review of Suspected Drug-Induced Liver Injury (DILI) In Nonalcoholic Steatohepatitis (NASH) Patients by a Panel of Pathologists and Hepatologists: Lessons Learned From the Seladelpar Hepatotoxicity Review Committee (SHRC)

1504

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CYMABAY THERAPEUTICS

BACKGROUND AND AIMS

Surveillance for hepatotoxicity relies on clinical status and liver tests as signs and symptoms suggestive of DILI. Liver biopsy is reserved for confirmation or exclusion of indefinite cases. This approach is useful for acute toxicity, but some drugs can cause chronic toxicity leading to cirrhosis without clinical or laboratory signs. NASH trials with baseline (BL) and end of treatment (EoT) biopsies might detect such cases.

In a seladelpar NASH study (NCT03551522), a study pathologist read BL biopsies for study eligibility. EoT biopsies were read by two study pathologists without rescoring baseline tissues. Atypical histology for NASH was noted in 42/152 EoT biopsies: Portal inflammation and interface hepatitis with plasma cells, bile duct injury/cholangitis, vascular changes, and other miscellaneous findings. However, there were no signs or symptoms of DILI (rash, jaundice, eosinophilia, etc.) reported and biochemical parameters (ALT, AST, GGT, bilirubin) were improved or stable during the study.

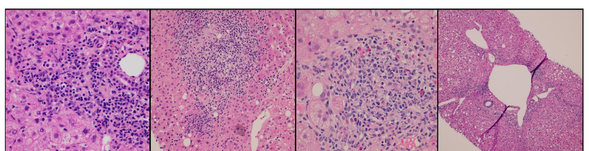
We describe our process for the adjudication of suspected chronic hepatotoxicity of seladelpar identified in EoT biopsies.

Atypical Findings in End of Treatment Biopsies

- 42 of 152 subjects with "atypical" findings

Atypical Findings at EoT	Placebo (n = 25)	Seladelpar 10 mg (n = 39)	Seladelpar 20 mg (n = 42)	Seladelpar 50 mg (n = 46)
Any Portal inflammation /Interface Hepatitis*	1 (4.0%)	3 (7.7%)	8 (19.0%)	11 (23.9%)
Any Bile Duct Injury†	3 (12.0%)	4 (10.3%)	5 (11.9%)	8 (17.4%)
Any Vascular Lesion‡	1 (4.0%)	2 (5.1%)	1 (2.4%)	4 (8.7%)
Other	1 (4.0%)	1 (2.6%)	1 (2.4%)	2 (4.3%)
Total (n = 42/152)	6 (24%)	8 (20.5%)	10 (23.8%)	18 (39.1%)

* Often with numerous plasma cells
† 3 granulomas were noted:
1 florid granulomatous duct lesion, 2 in placebo
‡ primarily portal vein extrusion



Interface hepatitis, plasma cells, eosinophils, and bile duct infiltrates	Epithelioid granulomatous cholangitis, interface hepatitis	Bile duct injury, plasma cells, eosinophils	Porto-sinusoidal vascular disease (PSVD)

- Findings described as atypical in NASH by study pathologists
- Concern: Treatment related? - higher incidence at seladelpar 50 mg
- Causality unknown
  - No biochemical signal
  - No evidence of hepatic decompensation or significant liver related adverse effects

METHODS

Seladelpar Phase 2b Study in NASH

Paired Liver Biopsy 52-Week Study Design

Liver fat ≥ 10%, NAS ≥ 4, F1 to F3, diabetes allowed

Baseline Biopsy → Placebo (n = 25) / Seladelpar 10 mg (n = 50) / Seladelpar 20 mg (n = 50) / Seladelpar 50 mg (n = 50) → End of Treatment Biopsy

Baseline (BL) Biopsy

- Single pathologist – Dr Guy
- NAS, portal inflammation, and fibrosis scored

End of Treatment (EoT) Biopsy

- Two pathologists blinded to treatment – Drs Guy and Brunt
- Baseline biopsies not re-read
- NAS, portal inflammation, and fibrosis scored
- 151 paired study biopsies were available for pathology review

Seladelpar Hepatotoxicity Review Committee Adjudication

Blinded Pathology Review

Two Blinded Rounds of Review

- Round 1 -- Baseline and EoT biopsies (302 singles)
  - Modified Ishak Histologic Activity Index (HAI)
  - Drs. Bedossa and Kleiner
- Round 2 -- Compare Baseline vs. EoT (151 pairs)
  - "Better, Same, Worse" (order blinded)
  - Interface hepatitis, portal inflammation, lobular inflammation, steatosis, ballooning, fibrosis, plasma cells, eosinophils, vascular injury, bile duct injury
  - Drs Bedossa, Goodman, and Kleiner

Case Review Teams

- No cases of suspected DILI identified in the blinded pathology review
- Adjudicated 42 cases from study pathologists
- Hepatologists: Drs Watkins (Chair), Maddrey, Kaplowitz
- Pathologists: Drs Bedossa, Goodman, Kleiner
- Experts: Drs Charlton (NASH) and Vierling (AIH/PBC)
- Each case prepared by 1 hepatologist & 1 pathologist

Clinical and Pathology Case Review

- Blinded to treatment
- Comprehensive clinical review:
  - Patient profile, NASH diagnosis, social history, medical history, treatment duration, key medications, clinical labs, immune and antibody markers, inflammation biomarkers, AEs
- Pathology findings:
  - Study pathologist findings
  - Review pathologist scores

SHRC Adjudication of Cases

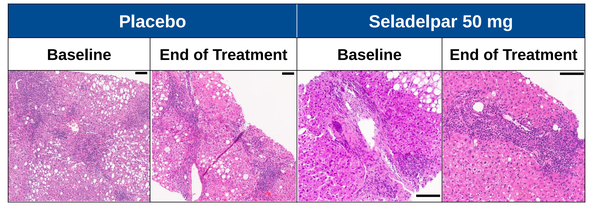
- Case adjudication
  - Clinical/biochemical evidence of DILI: YES/NO?
  - New/progressing liver histology: YES/NO?
  - If YES, causality assessment: not related, unlikely, possible, probable, highly likely study drug related

Unblinding Treatment

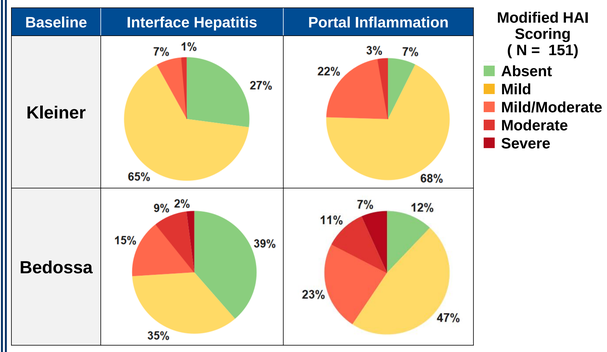
- SHRC was unblinded after adjudication

RESULTS

Histology: Baseline vs. End of Treatment



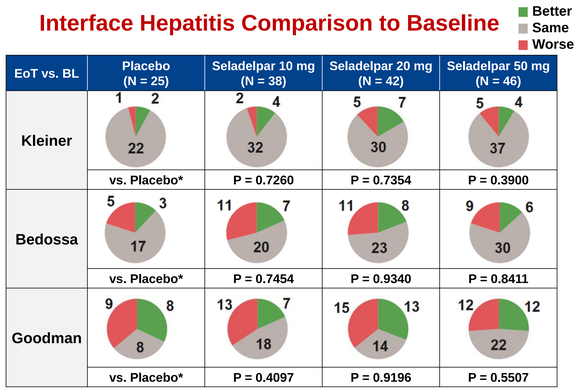
Prevalence Interface Hepatitis and Portal Inflammation



Prevalence of Plasma Cells, Eosinophils, Bile Duct Injury

Baseline	Plasma Cells	Eosinophils	Bile Duct Injury
Kleiner	7%	9%	1%
Bedossa	5%	6%	9%
Goodman	54%	15%	44%

Interface Hepatitis Comparison to Baseline



* P-value vs. Placebo by ordinal logistic regression

- Changes in portal inflammation (EoT vs. BL) were not significant and was not dose-related similar to interface hepatitis

SHRC Adjudication Results

- No clinical or biochemical evidence of DILI
- Atypical histology present in baseline biopsies without worsening on treatment in 69% (29/42)
- Causality assessed in 13 cases with evidence of a new or progressive unexpected liver pathology

Causality Assessment of 13 cases	Not Related 0-10% Causality	Unlikely < 25% Causality	Possible 25-49% Causality	Highly Likely 50-74% Causality	Probable 75-100% Causality
Placebo (n = 25)	0	2 (8%)	0	0	0
Seladelpar 10 mg (n = 39)	1 (2.6%)	2 (5.1%)	0	0	0
Seladelpar 20 mg (n = 42)	1 (2.4%)	2 (4.8%)†	0	0	0
Seladelpar 50 mg (n = 46)	1 (2.2%)	3 (6.5%)*	1 (2.2%)‡	0	0

* One 50 mg case was a split decision: 3 votes Unlikely and 3 votes Not Related
† One 20 mg case was a split decision: 5 votes Unlikely and 1 vote Possible
‡ Subject with long standing lupus and diverticulitis prior to biopsy

SHRC Unanimous Consensus Statement

- The features noted by study pathologists at end of treatment were confirmed on this review. However, these did not differ qualitatively between baseline and end of treatment. We suspect these histologic features are underreported; however, in the experience of the pathology review subcommittee these features may be observed in patients with NASH
- The panel unanimously concluded that the data in aggregate including the complete absence of clinical and biochemical evidence of drug-induced liver injury and the lack of significant differences in histologic features or their changes across the placebo and treatment groups do not support injury related to seladelpar
- The panel also unanimously supported lifting of the clinical hold and the reinitiation of clinical development

CONCLUSIONS

- No clinical, biochemical or histologic evidence that seladelpar is hepatotoxic
- Similar prevalence of atypical histologic features in baseline and end of treatment liver biopsies
- FDA clinical hold lifted after review of SHRC report
- Concurrent review of paired baseline and end of treatment biopsies is recommended
- Further understanding of portal area changes in NASH is needed

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