Kinase Inhibitor Induced Liver Injury

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INTRODUCTION

- Protein Kinase Inhibitors (KIs) are widely used, with >100 approved since 2003.
- While liver enzyme elevations are common, the features of **clinically apparent KI-induced liver injury (KILI)** remain unclear.
- KILI may have **drug-specific patterns, variable latency, and genetic predisposition**, but systematic data are limited.
- The **Drug-Induced Liver Injury Network (DILIN)** provides a resource to evaluate KILI.

Aim:

AIMS

- **To assess the frequency, clinical features, outcomes, and genetic associations** of KILI compared with non-KI DILI.

METHODS

- **Cases:** 1,553 suspected DILI (excluding Herbal and Dietary Supplements) → Analyzed as 33 KILI (probable/highly likely/definite) vs 1,520 non-KI DILI.
- **Clinical data:** demographics, drug, dose/indication, latency, injury pattern (R ratio), peak labs (ALT, ALP, bilirubin, INR), autoantibodies.
- **Outcomes:** Hospitalization, corticosteroid use, biopsy, transplant, death.
- **Histology:** Central review of available liver biopsies.
- **Genetics:** HLA sequencing in KILI and controls; associations tested statistically

RESULTS

1. **33 high causality cases (2.1%)** out of 1,553 in DILIN (2004–2024), attributed to KILI.
2. **Trends over time:** KILI frequency increased: **0.6%** (2004–2009) → **1.6%** (2010–2014) → **2.4%** (2015–2019) → **4.2%** (2020–2024).
3. **Causative drugs:**
   - **Imatinib** – 10 cases (30%).
   - **Pazopanib** – 5 cases (15%).
   - **Dabrafenib, Lapatinib, Ribociclib** – 2 cases each.
   - **12 other KIs** – 1 case each (Figure1).
4. **Phenotype:** 58% hepatocellular, 24% cholestatic, 18% mixed (Figure2).
5. **Hospitalization:** 11 patients (33%). 1 fatality (palbociclib).
6. **Rechallenge:** 6 patients re-exposed to the same KI. All recurred; 1 partial adaptation.
7. **Immune checkpoint inhibitor (ICI) exposure:** Recent ICI therapy (<150 days) preceded KILI in 15% of cases (5/33), indicating potential immune priming as a risk factor for kinase inhibitor hepatotoxicity.

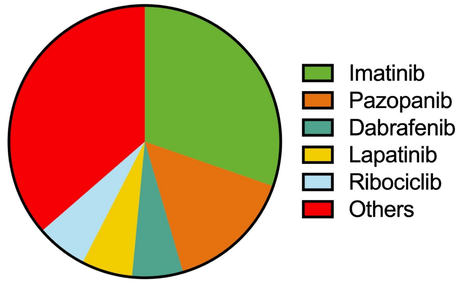

Figure 1: Causative Drug in Drug-Induced Liver Injury

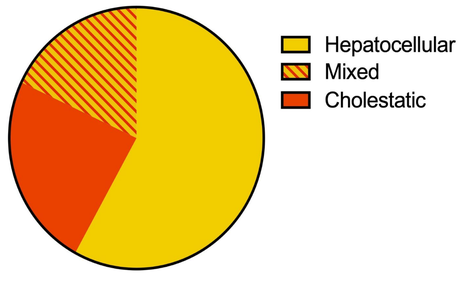

Figure 2: Clinical Phenotype Distribution

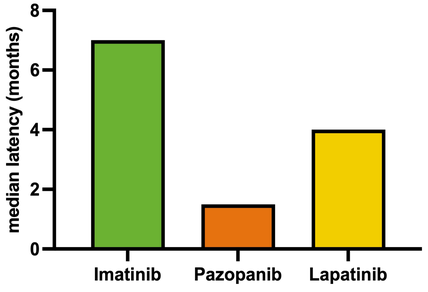

Figure 3: Latency by Drug

Allele 1	Allele 2	Allele 3	P-value	KILI Freq	DILIN Control Freq	Known Associations
DRB1*13:04	DRB3*02:02	-	3.8E-06	0.04	0.003	DRB3*02:02 Type 1 diabetes Graves' disease
DRB1*07:01	DRB4*01:01	-	0.0001	0.3	0.12	DRB1*07:01 Lapatinib DILI DRB4*01:01 AIH, PBC
DRB1*07:01	DQA1*02:01	-	<0.001	0.3	0.12	DQA1*02:01 Celiac disease
DRB1*07:01	DQA1*02:01	C*06:2	9.3E-07	0.2	0.04	C*06:02 Psoriasis

Table 1: Haplotype Frequencies in KILI vs. DILIN Controls and Autoimmune Associations

DISCUSSION

KILI is an emerging cause of liver injury, with rising incidence in DILIN over the past two decades, paralleling increased KI use. **Imatinib** was the most frequent culprit, showing a **hepatocellular, immune-mediated phenotype with long latency**, while **Pazopanib** and **Lapatinib** displayed distinct cholestatic vs hepatocellular patterns. **Clinical severity was notable**: one-third hospitalized, nearly half biopsied, and a fatal case occurred; rechallenge uniformly led to recurrence.

There were strong HLA associations (DQA1*02:01, DRB1*07:01, C*06:02) supporting **genetic susceptibility** and overlap with autoimmune disease risk alleles. ($P = 9.3\times10^{-7}$) (Table 1). These alleles are implicated in autoimmune diseases (AIH, celiac disease, psoriasis).
Recent ICI therapy (<150 days) preceded KILI in 15% of cases (5/33), indicating potential immune priming as a risk factor for kinase inhibitor hepatotoxicity.

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