



# METHYLPREDNISOLONE ASSOCIATED DRUG-INDUCED LIVER INJURY

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## INTRODUCTION

- Methylprednisolone (MP) is used in many conditions including autoimmune hepatitis.
- There are increasing reports that MP given in high doses intravenously is associated with hepatocellular injury particularly in patients with multiple sclerosis (MS), suggesting a rising incidence or a previously under-recognized entity.
- The Drug-Induced Liver Injury Network (DILIN) is a National Institutes of Health (NIH)-funded study that has been enrolling patients with suspected DILI in the United States since 2004.

## AIM

The aim of this study was to determine the clinical, histologic characteristics and HLA associations of MP-associated DILI in the United States DILI Network (DILIN).

## METHODS & RESULTS

- All adjudicated cases of suspected DILI enrolled in the DILIN Prospective Study between 2004-2020 where MP was listed as an implicated or concomitant medication were reviewed.
- All had standard DILIN causality scoring by expert consensus committee using a 5-point scale (1=definite, 2=highly likely, 3=probable, 4=possible, 5=unlikely) based on 6 months post-injury data.
- Two investigators (JA, JHH) independently re-analyzed the cases. Any cases identified as high confidence (HiCon) (scores of 1,2 and 3) but not initially adjudicated as such were sent back for readjudication by the causality committee.
- Clinical characteristics of HiCon cases were reviewed.
- HLA data from direct sequencing of all cases associated with MP and DILI due to other drugs were analyzed.

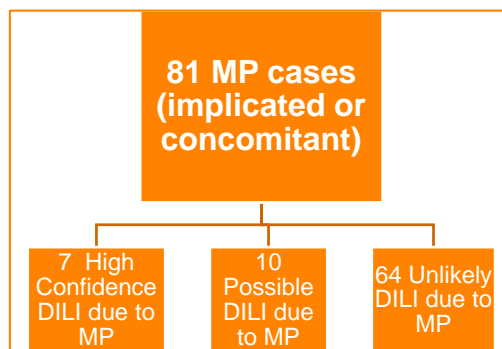
## RESULTS

- 81 cases with MP as implicated or concomitant medication were reviewed
- Total of 7 high confidence MP cases (1 definite, 2 highly likely, 4 probable)
- 6 initially adjudicated as high confidence
- 1 case adjudicated as possible sent back to committee and scored as highly likely
- 1 case in 2006, rest since 2011
- 6 of the 7 cases in patients with multiple sclerosis (MS)
- 10 possible MP cases (5 DILI from another drug with overall causality 1,2,3)
- 64 unlikely MP cases (51 DILI from another drug with overall causality 1,2,3)
- HLA data available on 5 of 7 HiCon MP cases, 48 of 56 possible/unlikely MP cases and 1226 controls (DILI due to other drugs)

Table 1: Clinical characteristics of 7 High Confidence MP DILI patients

Characteristic	Value	Range or %
Median Age (years)	47.8	18-69
Female sex	5	71%
Median BMI (kg/m <sup>2</sup> )	28.1	21.4-49.3
Median latency to DILI onset (days)	14	6-150
Median R value at onset	12.5	5-34.5
Median ALT at onset (U/L)	310	228-1694
Median total bilirubin at onset (mg/dL)	1	0.4-10.9
Severity		
Mild (1+)	3	43%
Moderate (2+ or 3+)	4	57%
Severe (4+) or Fatal (5+)	0	0%
Jaundice	3	43%
Rechallenge	1	

Figure 1: Flow Diagram of Review of 81 Suspected DILI Cases involving MP



Tables 2 and 3: Top HLA alleles and Individual HLA data on 5 High Confidence MP DILI cases

HLA allele	MP cases (N=5)		Compare to DILIN other drugs (n=1226)				Compare to Possible/Unlikely MP (n=48)			
	Case counts	CF	AF	P	AF fold change	AF	p	AF fold change		
C*07:02	4	0.8	0.4	0.13	0.035	3.00	0.10	0.026	3.84	
DQA1*01:02	5	1	0.6	0.23	0.012	2.67	0.22	0.016	2.74	
DQA1*03:01	3	0.6	0.3	0.17	0.388	1.78	0.06	0.038	4.80	
DQB1*03:02	2	0.4	0.2	0.09	0.242	2.13	0.02	0.044	9.60	
DQB1*06:02	5	1	0.6	0.16	0.002	3.82	0.15	0.003	4.12	
DRB1*15:01	3	0.6	0.4	0.14	0.038	2.93	0.14	0.053	2.95	

CF: carriage frequency; AF: allele frequency; P: p-value from Fisher exact test  
Both DQA1\*01:02 and DQB1\*06:02 presented in all 5 MP cases. These two alleles are common in the population (population AF=0.216 for DQA1\*01:02 and 0.115 for DQB1\*06:02)

## CONCLUSION

- MP DILI is characterized by hepatocellular injury with/without jaundice, short latency and rapid recovery.
- In DILIN, MP DILI was seen largely in MS patients where the complete or partial haplotype prevalent in the MS population HLA-DRB1\*15-HLA DQA1\*01:02-DQB1\*06:02 was present in all 5 HC MP cases tested.

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## CONTACT INFORMATION

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