Therapeutic management of idiosyncratic drug-induced liver injury and acetaminophen hepatotoxicity in the paediatric population: a systematic review

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Table S1. Characteristics and outcome of drug-induced liver injury in the paediatric population.

| Culprit drug      | Median age (range) | Sex | Drug start to DILI onset (median) | Severity of DILI at recognition (n) | DILI pattern (n) | Outcome (n) |
|-------------------|--------------------|-----|----------------------------------|-------------------------------------|-----------------|-------------|
|                   | Boy    | Girl|                                 |                                     |                 |             |
| **Preterm newborn neonates (from day of birth through the expected date of delivery plus 27 days)** | | | | | | |
| Acetaminophen     | 35 days           | 1   | 5 days                           | Severe                              | Hepatocellular  | Recovery    |
| (N=1)             |                   |     |                                 |                                     |                 |             |
| **Term and post-term neonates (from day of birth plus 27 days)** | | | | | | |
| Acetaminophen     | 4 days            | 1   | 1 day                            | Severe                              | NA              | Recovery    |
| (N=1)             |                   |     |                                 |                                     |                 |             |
| **Infants (or toddlers) (from 1 month [28 days] to 23 months)** | | | | | | |
| Acetaminophen     | 6 months          | 5   | 1 day                            | Severe (2)                          | Hepatocellular (2) | Recovery (6) |
| (N=7)             | (58 days – 18 months) | 2 | | ALF (2) | NA (5) | |
| **Children (from 2 years to 11 years)** | | | | | | |
| Acetaminophen     | NAa               | 4   | 1 day (N=3)                      | Mild (1)                            | NA (13)         | Recovery (13) |
| (N=13)            |                   |     |                                 | Moderate (2)                        |                 |             |
|                   | TMP-SMZ (N=4)     | 6   | 25 days                          | Severe (1)                          | Hepatocellular (1) | Recovery (3) |
|                   | (2 – 8 years)     | 2   |                                 | NA (3)                              | Cholestatic (1) | LTx (1)     |
|                   | Valproic acid     | 4.9 | 25 days                          | Severe (1)                          | Hepatocellular (14) | Death (14) |
| (N=15)            | (1.1 – 8.8 years) | 11  |                                 | NA (1)                              | NA (1)          | LTx (1)     |
|                   | Amoxicillin-      | 2 years 9 months | 1 | 24 days | NA | Cholestatic | LTx |
| clavulanate (N=1) |                    |     |                                 |                                     |                 |             |
|                   | **Adolescents (from 12 years to less than 18 years)** | | | | | |
| Acetaminophen     | 15.5 years        | 1   | 10 hours (N=1)                   | ALF (1)                             | NA (2)          | Recovery (1) |
| (N=2)             | (14 – 17 years)   |     |                                 | NA (1)                              |                 | LTx (1)     |
|                   | Valproic acid     | 15  | 11 years                         | NA (2)                              | Hepatocellular (2) | Death (2)  |
| (N=2)             | (12 – 17 years)   | 1   |                                 |                                     |                 |             |
|                   | TMP-SMZ (N=1)     | 17  | 28 days                          | Moderate                            | Hepatocellular  | Recovery    |
|                   | (N=1)             |     |                                 |                                     |                 |             |

ALF: acute liver failure; DILI: drug-induced liver injury; LTx: liver transplantation; NA: Not available; TMP-SMZ: trimethoprim-sulfamethoxazole.
* One child was two years old, six children were aged a median of 2.2 years old, one child was four years old, three children aged ≤5 years, one child was six years old, and the remaining child was aged nine years.
Table S2. Prospective and retrospective studies on idiosyncratic drug-induced liver injury in the paediatric population.

|                           | United States (n=57) | Spain (n=33) | India (n=39) | China (n=69) |
|---------------------------|----------------------|--------------|--------------|--------------|
| Age, years (median, range)| 14.3 (1.7-17.9)      | 2.7 (0.1-16) | 16 (2.6-17)  | 8 (0.2-14)   |
| Female, %                 | 67                   | 47           | 44           | 33           |
| Jaundice, %               | 53                   | -            | 79           | 59           |
| Fever, %                  | 37                   | -            | 41           | 32           |
| Rash, %                   | 25                   | -            | 41           | 22           |
| Hospitalization, %        | 63                   | -            | 82           | 100          |
| Duration of therapy (median) (days) | 55                 | 9.5         | 30           | -            |
| Liver injury pattern, %   |                      |              |              |              |
| Hepatocellular            | 82                   | 56           | 54           | 90           |
| Cholestatic               | 8                    | 19           | 26           | 2.9          |
| Mixed                     | 10                   | 25           | 21           | 7.2          |
| Major culprit drugs, %    | Minocycline (19);    | Amoxicillin-clavulanate (31); | Anti-tuberculous drugs (22); | Chinese herbal medicines (22); |
|                           | valproate (11);      | ibuprofen, | phenytoin (10); | anti-tuberculosis agents, macrolides (8.7) |
|                           | azithromycin,        | isoniazid (8.3) | carbamazepine (5) | |
|                           | trimethoprim-        |               |              |              |
|                           | sulfamethoxazole (7.0) |          |              |              |
| Causality assessment method | CIOMS/RUCAM          | CIOMS/RUCAM | CIOMS/RUCAM  | CIOMS/RUCAM  |
| Liver parameters at DILI recognition, median (range) | Aspartate aminotransferase (IU/L) | 380 (26-3,400) | -             | 258 (25-1,857) | 434 (145-968) |
|                           | Alanine aminotransferase (IU/L) | 411 (33-4,185) | -             | 323 (12-5,647) | 649 (215-1,125) |
|                           | Alkaline phosphatase (IU/L) | 203 (62-1,177) | -             | 258 (81-1,695) | 287 (224-419) |
| Total bilirubin (mg/dL)   | 3.3 (0.2-34)         | -            | 5.1 (0.7-31) | 4.1 (0.5-14.8) |
| INR                       | 1.2 (0.9-3.9)        | 1.5 (0.8-12) | -            |              |
| Severity, %               |                      |              |              |              |
| Mild                      | 35                   | -            | -            |              |
| Moderate                  | 41                   | -            | -            |              |
| Severe                    | 19                   | 5.6         | -            |              |
| Fatal/liver transplant    | 5                    | 2.8         | 31           | 8.7          |
| Liver-related death, n (%)| 0 (0)                | 1 (2.8)     | 12 (31)      | 2 (2.9)      |
| Liver transplantation, n (%)| 3 (5)              | 1 (2.8)     | 0 (0)        | 0 (0)        |

Anti-tuberculosis drugs: isoniazid, rifampicin, pyrazinamide and ethambutol; CIOMS/RUCAM: Council for International Organizations of Medical Sciences / Roussel Uclaf Causality Assessment Method; INR: International Normalized Ratio; macrolides: azithromycin, roxithromycin.

a Data from the Drug Induced Liver Injury Network (DILIN).
b There were 36 DILI episodes. Three episodes were accidental re-exposure. Percentages are based on the number of DILI episodes.
c Data from single-center studies.
d Severity of DILI in 18% of cases was moderate, and for the 23% of cases were moderate-hospitalized.

Data collected from hospitalized patients.
f Peak values. Data are presented as median and interquartile range.