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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **RUCAM items with attribution of scores (SC)** | **CASES 1-26** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **SC** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** | **15** | **16** | **17** | **18** | **19** | **20** | **21** | **22** | **23** | **24** | **25** | **26** |
| **1. Time to onset from the**  **beginning of the herb**  5 – 90 days  < 5 or > 90 days | **+2**  **+1** | **+2** | **+2** | **+2** | **+2** | **+2** | **+2** | **+2** | **+2** | **+2** | **+2** | **+2** | **+2** | **+2** | **+2** | **+2** | **+2** | **+2** | **+2** | **+2/+2** | **+2** | **+2** | **+2** | **+2** | **+2** | **+2** | **+2** |
| **Alternative: Time to onset from**  **cessation of the herb**  ≤ 15 days | **+1** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **2. Course of ALT after cessation of**  **the herb**  Decrease ≥ 50 % within 8 days  Decrease ≥ 50 % within 30 days  No information of continued drug use  Decrease ≥ 50 % after the 30th day  Decrease < 50 % after the 30th day  or recurrent increase | **+3**  **+2**  **0**  **0**  **-2** | **+2** | **+2** | **+2** | **+2** | **0** | **0** | **+2** | **+2** | **+2** | **+3** | **0** | **+2** | **+2** | **+3** | **+2** | **+2** | **+3** | **+2** | **+3/+3** | **+2** | **+2** | **+3** | **+2** | **+2** | **+2** | **+2** |
| **3. Risk factors**  Alcohol use [current drinks/d: > 2 for  woman, > 3 for men]  Alcohol use [current drinks/d: ≤ 2 for  woman, ≤ 3 for men] | **+1**  **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0/0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** |
| Age ≥ 55 years  Age < 55 years | **+1**  **0** | **0** | **+1** | **+1** | **0** | **+1** | **+1** | **+1** | **+1** | **+1** | **0** | **+1** | **+1** | **+1** | **0** | **0** | **+1** | **0** | **0** | **+1/+1** | **0** | **+1** | **0** | **0** | **0** | **0** | **+1** |
| **4. Concomitant drug[s]/herb[s]**  None or no information  Concomitant drug/herb with incompatible time to onset  Concomitant drug/herb with compatible or suggestive time to onset  Concomitant drug/herb known as hepatotoxin and with compatible or suggestive time to onset  Concomitant drug with evidence for its role in this case [positive rechallenge or validated test] | **0**  **0**  **-1**  **-2**  **-3** |  | **-2** | **0** | **0** | **-2** | **-2** | **0** | **-2** | **-1** | **-2** | **-2** |  | **0** | **0** | **0** | **0** | **0** | **0** | **0/0** | **0** | **0** | **-2** | **0** | **-1** | **-1** | **-2** |
| **5. Search for alternative causes**  **Group I [7 causes]**  HAV: Anti-HAV-IgM  HBV: Anti-HBC-IgM, HBV-DNA  HCV: Anti-HCV, HCV-RNA  HEV: Anti-HEV-IgM, anti-HEV-IgG, HEV-  RNA,  Hepatobiliary sonography/colour Doppler  sonography of liver vessels / endo-  sonography/CT/MRC  Alcoholism  Acute recent hypotension history  [particularly if underlying heart disease]  **Group II [5 causes]**  Complications of underlying disease[s]  such as sepsis, metastatic malignancy,  autoimmune hepatitis, chronic hepatitis B  or C, primary biliary cholangitis or  sclerosing cholangitis, genetic liver  diseases  Infection suggested by PCR and titre  change for  CMV [anti-CMV-IgM, anti-CMV-IgG]  EBV [anti-EBV-IgM, anti-EBV-IgG]  HSV [anti-HSV-IgM, anti-HSV-IgG]  VZV [anti-VZV-IgM, anti-VZV- IgG]  **Evaluation of group I and II**  All causes - groups I and II - reasonably  ruled out  The 7 causes of group I ruled out  6 or 5 causes of group I ruled out  Less than 5 causes of group I ruled out  Alternative cause highly probable | **+2**  **+1**  **0**  **-2**  **-3** | **Ø Ø**  **Ø**  **Ø**  **Ø**  **N**  **N**  **N**  **Ø**  **Ø**  **Ø**  **Ø**  **-2** | **Ø**  **Ø**  **Ø**  **Ø**  **Ø**  **N**  **N**  **N**  **Ø**  **Ø**  **Ø**  **Ø**  **-2** | **N**  **N**  **N**  **Ø**  **Ø**  **N**  **N**  **N**  **Ø**  **Ø**  **Ø**  **Ø**  **0** | **N**  **N**  **Ø**  **Ø**  **Ø**  **N**  **N**  **N**  **Ø**  **Ø**  **Ø**  **Ø**  **0** | **Ø**  **Ø**  **Ø**  **Ø**  **Ø**  **N**  **N**  **Ø**  **Ø**  **Ø**  **Ø**  **-2** | **N**  **N**  **N**  **Ø**  **Ø**  **N**  **N**  **N**  **Ø**  **Ø**  **Ø**  **Ø**  **0** | **Ø**  **Ø**  **N**  **Ø**  **Ø**  **N**  **N**  **N**  **Ø**  **Ø**  **Ø**  **Ø**  **-2** | **Ø**  **Ø**  **Ø**  **Ø**  **Ø**  **N**  **N**  **N**  **Ø**  **Ø**  **Ø**  **Ø**  **-2** | **Ø**  **Ø**  **Ø**  **Ø**  **Ø**  **N**  **N**  **N**  **Ø**  **Ø**  **Ø**  **Ø**  **-2** | **Ø**  **Ø**  **Ø**  **Ø**  **Ø**  **N**  **N**  **N**  **Ø**  **Ø**  **Ø**  **Ø**  **-2** | **N**  **N**  **Ø**  **Ø**  **N**  **N**  **N**  **Ø**  **Ø**  **Ø**  **Ø**  **-2** | **N**  **N**  **N**  **Ø**  **Ø**  **N**  **N**  **N**  **Ø**  **Ø**  **Ø**  **0** | **N**  **N**  **Ø**  **Ø**  **N**  **N**  **N**  **Ø**  **Ø**  **Ø**  **Ø**  **-2** | **N**  **N**  **N**  **Ø**  **N**  **N**  **N**  **N**  **Ø**  **Ø**  **Ø**  **Ø**  **0** | **Ø**  **Ø**  **Ø**  **Ø**  **Ø**  **N**  **N**  **N**  **Ø**  **Ø**  **Ø**  **Ø**  **-2** | **Ø**  **Ø**  **Ø**  **Ø**  **Ø**  **N**  **N**  **N**  **Ø**  **Ø**  **Ø**  **Ø**  **-2** | **N**  **N**  **N**  **Ø**  **Ø**  **N**  **N**  **N**  **Ø**  **+**  **Ø**  **Ø**  **0** | **N**  **N**  **N**  **Ø**  **Ø**  **N**  **N**  **N**  **Ø**  **Ø**  **Ø**  **Ø**  **0** | **Ø/Ø**  **Ø/Ø**  **Ø/Ø**  **Ø/Ø**  **Ø/Ø**  **N/N**  **N/N**  **N/N**  **Ø/Ø**  **Ø/Ø**  **Ø/Ø**  **Ø/Ø**  **-2/-2** | **Ø**  **Ø**  **Ø**  **Ø**  **Ø**  **N**  **N**  **N**  **Ø**  **Ø**  **Ø**  **Ø**  **-2** | **Ø**  **Ø**  **Ø**  **Ø**  **Ø**  **N**  **N**  **N**  **Ø**  **Ø**  **Ø**  **Ø**  **-2** | **Ø**  **N**  **N**  **Ø**  **Ø**  **N**  **N**  **N**  **Ø**  **Ø**  **Ø**  **Ø**  **-2** | **Ø**  **Ø**  **Ø**  **Ø**  **Ø**  **N**  **N**  **N**  **Ø Ø**  **Ø**  **Ø**  **-2** | **Ø**  **Ø**  **Ø**  **Ø**  **Ø**  **N**  **N**  **N**  **Ø**  **Ø**  **Ø**  **Ø**  **-2** | **N**  **N**  **Ø**  **Ø**  **Ø**  **N**  **N**  **N**  **Ø**  **Ø**  **Ø**  **Ø**  **0** | **Ø**  **Ø**  **Ø**  **Ø**  **Ø**  **N**  **N**  **N**  **Ø**  **Ø**  **Ø**  **Ø**  **-2** |
| **6. Previous information on**  **hepatotoxicity of the herb**  Reaction labelled in the product  characteristics  Reaction published but unlabelled  Reaction unknown | **+2**  **+1**  **0** | **+2** | **+2** | **+2** | **+2** | **0** | **+2** | **+2** | **+1** | **+2** | **+2** | **0** | **+2** | **+2** | **+2** | **+2** | **+2** | **+2** | **+2** | **+2/+2** | **+2** | **+2** | **+2** | **+2** | **+2** | **+2** | **+2** |
| **7. Response to unintentional**  **reexposure**  Doubling of ALT with the herb alone,  provided ALT below 5 ULN before  reexposure  Doubling of ALT with the herb already  given at the time of first reaction  Increase of ALT but less than ULN in the  same conditions as for the first  administration  Other situations | **+3**  **+1**  **-2**  **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **+1** | **0** | **0** | **0** | **0** | **0** | **0** | **0** |
| **Total score for case** |  | **4** | **3** | **7** | **6** | **-1** | **3** | **5** | **3** | **4** | **3** | **-1** | **7** | **5** | **7** | **4** | **5** | **6** | **6** | **6/7** | **4** | **5** | **3** | **4** | **6** | **5** | **3** |

**Total score for causality**: ≤ 0 / excluded; 1-2 / unlikely; 3-5 / possible; 6-8 / probable; ≥ 9 / highly probable

**Causality assessment for cases 1 – 26 of the liver injury study cohort, using the updated RUCAM25** Considered were the items for the hepatocellular type of liver injury and the data of 26 patients with normal ALT values at hospital admission, who experienced elevated ALT levels > 5 x ULN after use of herbal TCM. In the above section 4 (part 1 of the tabula) of concomitant drug[s], the following TCM herbs and drugs were considered. In the section 5 [search for alternative causes in part 2 of the tabula], the symbol of (N) denotes that the obtained result was negative, whereas (Ø) indicates that assessment was not performed.

**Abbrevations:** ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; CT: Computed tomography; HAV: Hepatitis A Virus; HBc: Hepatitis B Core; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; CMV: Cytomegalovirus; EBV: Epstein Barr Virus; HEV: Hepatitis E Virus; HSV: Herpes Simplex Virus; MRC: Magnetic resonance cholangiography; PCR: Polymerase Chain Reaction; RUCAM: Roussel Uclaf Causality Assessment Method; ULN: Upper Limit Normal; VZV: Varicella Zoster Virus