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CORRESPONDENCE

Letter to the editor: Concerning the paper entitled "TC (Giloy) induced liver injury…" by Anand Kulkarni et al.

Concerning the paper entitled "TC (Giloy) induced liver injury…" by Anand Kulkarni et al.,[1] the paper is built on a completely unscientific foundation.

1. There is insufficient data to rule out other causes:
   a. There were 43 patients in the study with 79 distinct comorbidities among them; median age of 54 years indicates older patients on polypharmacy over longer durations. Excluding drug-induced liver injury (DILI) and singling out Tinospora cordifolia (TC) as inducing herb-induced liver injury (HILI) is highly questionable.
   b. Known risk factors, including human leukocyte antigen genotype, autoimmune hepatitis triggers, and contraceptive use, are not reported.
   c. There is high variability in duration (5–362 days), dosage (15–90 ml/day), dosage forms, and brands of TC consumed.
   d. Statistically significant causation cannot be established because the population set is not specified. A sample of 43 was drawn from how many patients consuming Giloy, across 13 locations and 15 months? In India, prevalence data as low as 1.3% of HILI has been reported among DILI cases.[2]
2. There are methodology flaws in the clinical diagnosis of HILI:
   a. There is no evidence of compliance with the "updated RUCAM Guidelines"[3]
      (i) Inclusion of pre-existing chronic liver disease (56% of sample);
      (ii) Nonexclusion of hepatic injury before TC use, such as nonhepatic elevation of alkaline phosphatase (ALP); and
      (iii) Unavailable RUCAM scores for co-administered drugs.
   b. RUCAM is more accurate if used prospectively and for idiosyncratic reactions. This study is retrospective and includes both intrinsic and idiosyncratic liver injury. Furthermore, from a clinical perspective, it is easier to identify the intrinsic etiological agent rather than idiosyncratic reactions.[3]
   c. Liver biopsy is not used routinely for HILI diagnosis and management.[4]
   d. Both HILI and DILI are difficult and complex to diagnose and are often misdiagnosed. Definitive diagnosis of HILI requires latency period, clinical presentation, patient's risk factors for development of HILI, biochemistry alterations especially in alanine aminotransferase (ALT) and ALP, patient's medication(s), course of recovery (with dechallenge), and thorough search for other causes of liver disease.[4]
   e. There is neither baseline data nor time-series assessments for establishing a correlation with Giloy consumption, and there is no dechallenge data.
3. There are limitations to multicenter, retrospective studies[5] (13 locations, 15 months). With a huge variance in patient profiles, "possible cause" and "probable cause" attributions in a retrospective study generate a serious risk of observer bias. Furthermore, generally, in retrospective studies, while association may be inferred, causation may not be.

HILI is a subject worth serious, systematic study. Therefore, a prospective study with robust methodology that establishes statistically significant correlation of causation is mandatory. This esteemed journal must retract this prebiased, unscientific paper.

CONFLICT OF INTEREST

R.V. owns stock in and is an employee of Kerala First Health Services Pvt. Ltd.

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