JHEP|Reports

Reply to: "Ductular reaction is a prognostic factor in primary biliary cholangitis"

Ductular reaction as a putative tissue biomarker for staging and prognosis in primary biliary cholangitis

To the Editor:

We are pleased that Tan Y. and colleagues found interest in our study. In their letter to the *Journal*,[1] they aimed to confirm our observations on ductular reaction (DR) in a monocentric cohort of individuals with primary biliary cholangitis (PBC).

Tan Y. and colleagues reported an association between DR degree and the risk of developing severe adverse events in their cohort. This observation is in line with our study in *JHEP Reports*,[2] and it further confirms our previous findings on the relationship between DR and surrogate markers of outcome (*i.e.* response to UDCA therapy after 1 year, and prognostic scores of disease progression) in chronic cholangiopathies.[3,4]

The origin of DR is highly debated, including liver progenitor and mature cells (*i.e.* hepatocytes and cholangiocytes).[5] Nevertheless, abundant evidence points to the activation of DR as a driver of fibrogenesis and disease progression in several human liver and biliary tree diseases. Interestingly, severe or prolonged damage to parenchymal cells seems to be mandatory for determining the appearance of DR. Despite the controversial capability of this cellular response to support tissue repair,[6] there is an indisputable association between DR and advanced disease stage, irrespective of disease etiology. Indeed, the activation of profibrogenetic pathways by DR can fuel inflammation and fibrosis,[5] ultimately representing a tissue hallmark for active fibrogenesis.

Alkaline phosphatase (ALP) is a widely validated biomarker in PBC and is used as a level III surrogate endpoint in clinical trials in PBC. The ALP improvement in response to choleretic therapies, *e.g.* ursodeoxycholic acid (UDCA) and obeticholic acid (defined by several response criteria),[7] has been proven to be associated with overall survival in historical cohorts.[8,9] Unexpectedly, Tan Y. and colleagues did not find a significant association between ALP levels and the risk of severe adverse events. Moreover, they did not observe a direct correlation between DR and ALP levels. These observations disagree with the current consensus on the prognostic role of ALP levels in patients with PBC. The limited clinical characterization of their patient cohort (*e.g.* therapy regimen, timing of the liver biopsy, short-term follow-up, median levels of cholestatic and inflammatory biochemical markers), the lack of methodological details (modelling of ALP), and the inclusion of individuals with undefined overlap with autoimmune hepatitis demand that their findings be interpreted with caution.

In our study, we focused on biopsies obtained from individuals before UDCA administration and we excluded patients with an overlap syndrome. Remarkably, administration of therapeutic regimens (including UDCA) could remodel DR by restoring ductular-canalicular junctions as demonstrated in rodent models,[2,10] thus strengthening the importance of selecting a population naïve to UDCA therapy.

In conclusion, the observations of Tan Y and colleagues support the role of DR as a valid predictor of patient prognosis in individuals with PBC. Therefore, the quantification of DR on liver biopsy might represent a relevant tissue biomarker for staging and prognostic purposes.

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Conflict of interest

The Authors declare that there is no conflict of interest.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

All authors had contributed in writing and editing the manuscript.

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Supplementary data

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Author names in bold designate shared co-first authorship.

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Guido Carpino[1,*]
Vincenzo Cardinale[2,#]
Marco Carbone[3,#]

[1]*Department of Anatomical, Histological, Forensic Medicine and Orthopedic Sciences, Sapienza University of Rome, Rome, 00161, Italy;*
[2]*Department of Medico-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Latina, 04100, Italy;*
[3]*Division of Gastroenterology, Center for Autoimmune Liver Diseases, Department of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy and European Reference Network on Hepatological Diseases (ERN RARE-LIVER), San Gerardo Hospital, Monza, Italy*

[#]*Contributed equally.*

[*] Corresponding author. Address: Department of Anatomical, Histological, Forensic Medicine and Orthopedic Sciences, Sapienza University of Rome, Via Alfonso Borelli 50, 00161, Rome, Italy. Tel.: +39.06.49918062.
E-mail address: guido.carpino@uniroma1.it (G. Carpino).