



Hepatic fat and liver volume reductions impact on non-alcoholic steatohepatitis trials and potential solutions using qFibrosis and qBallooning

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Background and Aims

- Experimental treatment of non-alcoholic steatohepatitis (NASH) leads to reduction of hepatic fat and liver volume (LV) as assessed by magnetic resonance imaging-proton density fat fraction (MRI-PDFF).
- The impact of hepatic fat and LV reduction on histological fibrosis interpretation using the CRN system remains unexplored.
- Aim: To analyze the concomitant changes of qFibrosis (qF) and qSteatosis (qS) in zonal regions to evaluate the impact of hepatic fat and LV reduction on fibrosis changes, as well explore its impact on ballooning in patients with NASH.

Methods

- NASH patients were included from two phase 2b studies: 24-week study of Aldafermin (NCT02443116) and 36-week study of Resmetirom (NCT02912260).
- Steatosis correction (SC) was done by subtracting the steatosis area as detected by qS from total tissue area followed by an analysis of zonal fibrosis in the respective zones 1, 2, and 3.
- Concomitant fibrosis with drug-induced steatosis and ballooning changes were evaluated by co-localization of qF changes around qS and qBallooning (qB), respectively.

Results

COHORT 4: Results from the 24-Week Phase 2 Study of Aldafermin

- 78 patients with NASH randomly assigned (1:2) to groups given placebo (n=25) or Aldafermin 1 mg (n=53) daily for 24 weeks.
- Figure 1B:** qF continuous measures revealed 54% fibrosis regression in the treated group versus 19% in placebo group (p=0.007).
- Significant hepatic fat reduction, and trend for both fibrosis improvement and NASH resolution were observed for the COHORT 4 study.

- With qSteatosis, we applied steatosis correction to evaluate the impact of hepatic fat reduction on fibrosis.
- Figure 2:** With steatosis correction, zonal qF assessment showed trends of fibrosis reduction in portal, periportal (p=0.02) and zone 2 regions.

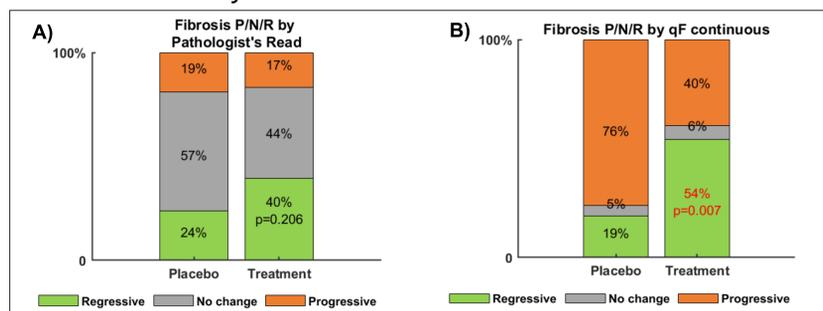
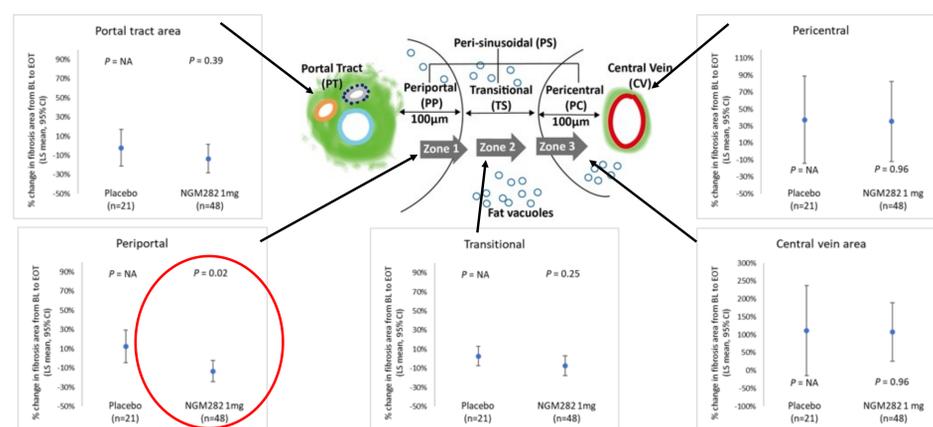


Figure 1: Progression/No change/Regression (P/N/R) plots according to (A) CRN versus (B) qFibrosis continuous value.



*All parameters were corrected by steatosis area

Figure 2: Zonal fibrosis assessment using steatosis tissue area correction for COHORT 4 study. Statistically significant fibrosis improvement in peri-portal zone is observed (circled red).

Phase 2 36-Week Study of Resmetirom in Patients with NASH

- Retrospective analysis was conducted on 102 paired biopsy samples and based on the liver volume reduction measured on serial MRI-PDFFs, corrections of qFibrosis were made for liver volume reduction.
- Figure 3A:** In Resmetirom-treated patients with reduced qSteatosis score, we observed statistically significant steatosis reduction with concomitant fibrosis improvement in Zone 2.
- Figure 3B:** LV correction was applied, and we observed **greater reduction** in concomitant fibrosis, with significant zonal steatosis reduction across **Zones 1, 2 and 3**.

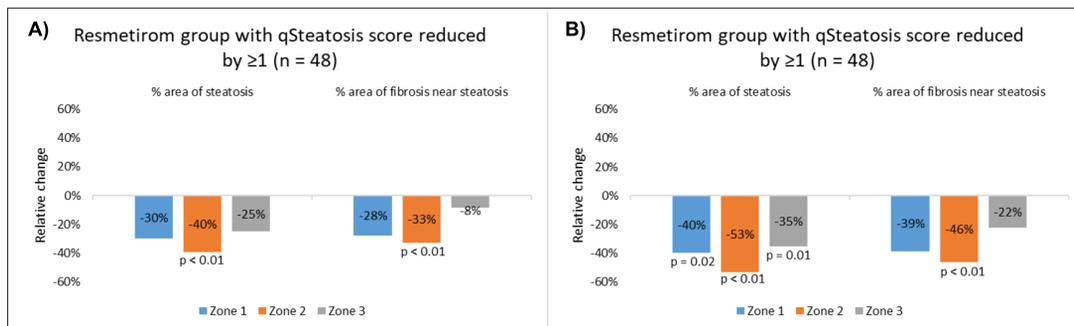


Figure 3: qFibrosis and qSteatosis colocalization analysis showing consistent fibrosis reduction with steatosis in treated group with (A) pre-LV correction, and (B) post-LV correction.

- Figures 4A, 4B:** In contrast, concomitant fibrosis changes observed around ballooning is **less sensitive to LV reduction**.

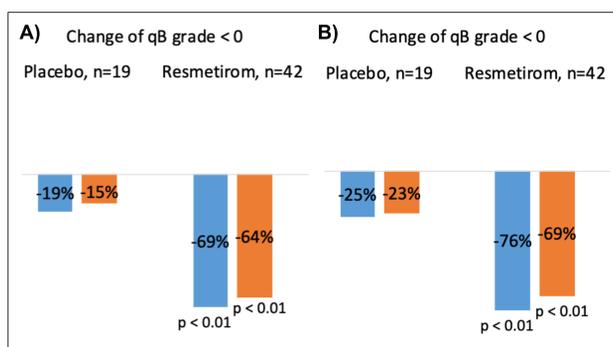


Figure 4: qFibrosis and qBallooning colocalization analysis reveals (A) fibrosis reduction in treated patients show more consistent trends at pre-LV correction. (B) But post-LV correction reveals concomitant fibrosis changes is less sensitive to LV reduction.

- Figure 5:** Further qB analysis to examine the correlation of ballooning reduction with fibrosis changes revealed an association between 1-stage fibrosis reduction with a relative change in qB area. The performance of applying -30.46% cut-off for relative change in qB area to predict 1-point reduction is shown in **Table 1**.

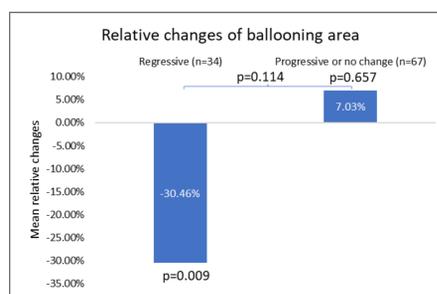


Figure 5: Area of ballooned hepatocytes is correlated with a 1-point reduction in fibrosis.

| Cut-off value for relative change of ballooning area | Validation results on COHORT 4 |
|--|--------------------------------|
| Cut-off = -30.46% | |
| Sensitivity | 50% |
| Specificity | 58% |
| Positive predictive value (PPV) | 39% |
| Negative predictive value (NPV) | 68% |

Table 1: The performance of ballooning area for predicting 1-point reduction was 50% sensitivity, 58% specificity with 39% PPV and 68% NPV.

Conclusion

- Application of SC and LV correction, along with qF and qS concomitant analyses with digital pathology can augment the interpretation of the mechanism of action of drugs in NASH, allowing for a better understanding of the impact of hepatic fat reduction on fibrosis regression in NASH.
- It is critical to consider these issues in future trials, and further validation work is ongoing.