Newsroom

Advancing Gene Therapy to Address Deafness

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Gene Therapy for Genetic Hearing Loss

How is gene therapy used to treat hearing loss?

The first gene therapy being tested for hearing loss seeks to replace the nonfunctioning *OTOF* gene in the cochlea with a working copy of the *OTOF* gene. This gene was selected because of its important role in the hearing process.

Gene therapy for children with *OTOF* gene-related deafness seeks to restore hearing by injecting copies of normal OTOF genes into the inner ear. With normal *OTOF* genes, the sensory cells will be able to function so they can respond to sound and activate the auditory nerve to send impulses to the brain. Functioning *OTOF* genes are encased in a viral vector, a modified form of a non-disease-causing virus, so they can be delivered into cochlear cells in the inner ear. This is an [in vivo gene therapy].

Because the cochlea is encased on a bony chamber that is difficult to reach, the gene therapy is delivered to the inner ear using a special device, in a minimally invasive surgical procedure developed at Children's Hospital of Philadelphi
ge therapy is placed into the inner ear using a device called an endoscope that lifts up the ear drum, allowing a
e to reach the "round window," a tiny area that leads to the cochlea. A single, very small dose of normal *OTOF* genes is

Research article

JHEP|Reports

Persistent risk of hepatocellular carcinoma despite improvement of liver stiffness in patients with chronic HBV with advanced fibrosis

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Background & Aims: Patients with chronic HBV (CHB) with advanced fibrosis are at high risk for hepatocellular carcinoma (HCC). Liver stiffness measurement (LSM) correlates with fibrosis in untreated patients, and is used to monitor changes in severity of liver disease. However, the association between on-treatment LSM and HCC risk is controversial.

Methods: We conducted an international multicenter retrospective cohort study of patients with CHB with advanced fibrosis and assessed the association between on-treatment LSM, HCC development, and decompensation events.

Results: We analyzed 562 patients (62.8% F4 LSM measurement, 69.2% Asian). During antiviral therapy, the on-treatment LSM decreased to <6 kPa in 209 (37.2%), to 6–9 kPa in 174 (31.0%), and remained >9 kPa in 179 (31.9%) patients. During a median follow-up of 6.8 years after the on-treatment LSM, 56 patients developed HCC and 18 (32.2%) had an on-treatment LSM <6 kPa. The 5-year cumulative HCC incidence was comparable across on-treatment LSM strata; 4.4% for <6 kPa, 5.5% for 6–9 kPa, and 5.8% for >9 kPa (p = 0.300). In multivariable analysis, older age (adjusted hazard ratio (aHR) 1.058, 95% CI 1.026–1.091, p <0.001) and lower platelet count (aHR 0.992, 95% CI 0.992–0.998, p = 0.005) were associated with HCC development, whereas on-treatment LSM was not (aHR 0.974, p = 0.974). By contrast, patients with an LSM decrease to ≤9 kPa had a negligible risk of decompensation (0% *vs.* 1.8% at 5 years, p = 0.017).

Conclusions: Most patients with CHB with advanced fibrosis experienced a decrease in LSM during antiviral therapy. Although a decrease in liver stiffness was associated with a lower risk of decompensation, an improvement in liver stiffness was not associated with a reduction in HCC risk.

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Highlights:

- Patients with CHB with advanced fibrosis are at high risk for HCC.
- Most patients with CHB experienced a decrease in LSM after initiation of antiviral therapy.
- The 5-year cumulative HCC incidence was comparable across on-treatment LSM strata.
- HCC surveillance should be continued in patients with advanced fibrosis before antiviral therapy regardless of on-treatment LSM values.

Impact and implications:

The majority of CHB patients with advanced fibrosis have a decrease in LSM during antiviral therapy. Although a decrease in LSM was associated with a lower risk of subsequent hepatic decompensation, an improvement in LSM was not associated with a reduction in HCC risk. HCC surveillance should therefore be continued in patients with advanced fibrosis at baseline regardless of LSM values obtained during therapy.

finding requires further confirmation.

In conclusion, most patients with CHB with advanced fibrosis experienced a decrease in LSM during antiviral therapy. Unfortunately, although this improvement in LSM was associated with a reduced risk of subsequent decompensation events, it was not associated with a clinically relevant reduction in the risk of HCC. Therefore, baseline fibrosis stage and not on-treatment LSM should be used to guide HCC surveillance strategies.

7. Ananthakrishnan AN, et al. J Gen Intern Med 2010;25:1164–1171.
8. Hong YR, et al. Gastro Hep. Adv 2023;2:810–817.

Conflicts of interest
This author discloses the following: Arun B. Jesudian has served on speaker bureaus for Madrigal Pharmaceuticals and as a consultant and on speaker bureaus for Mallinckrodt Pharmaceuticals and Salix Pharmaceuticals. The remaining authors disclose no conflicts.

Most current article

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Visualization Score Might Be Considered for Hepatocellular Carcinoma Surveillance

Dear Editors:

We read with interest the recent randomized trial by Rhee et al[1] comparing noncontrast magnetic resonance imaging (NC-MRI) and ultrasonography (US) for hepatocellular carcinoma (HCC) surveillance in cirrhotic patients. The study highlights the potential advantages of NC-MRI, including earlier stage detection at initial diagnosis and reduced false-positive referrals compared to US. Although this work represents a significant contribution to HCC surveillance strategies, we respectfully raise several points for consideration to strengthen the interpretation and clinical applicability of the findings.

According to an American Gastroenterological Association clinical practice update on screening and surveillance for HCC in patients with nonalcoholic fatty liver disease (NAFLD), US is highly accurate as well as cost-effective for detecting HCC in liver cirrhosis patients with a good that patients with suboptimal US (VIS-B or VIS-C) are at higher risk of HCC and higher odds of false-negative rates,[4] which suggests that the baseline US VIS is a relevant indicator for predicting the risk of subsequent HCC and can be used to assess the diagnostic performance of US surveillance in detecting HCC. It is suggested to compare false-positive rater referral in more detail for NC-MRI and US (VIS-A).

Although NC-MRI outperforms US in the surveillance of cirrhotic patients, its cost and accessibility should not be ignored. As Kim et al[5] highlighted, combining biannual US with NC-MRI achieved optimal sensitivity (83.9% to 85.0%) while balancing resource use. A US VIS-based approach with abbreviated magnetic resonance imaging (aMRI) was used in patients with NAFLD cirrhosis to analyze the cost-effectiveness of HCC screening. aMRI was used in patients with VIS-C and US negative for lesions, whereas US alone was applied in patients with VIS A/B. The US plus VIS strategy was less costly and only slightly less effective than screening with US alone. Therefore, a US VIS-based approach to incorporate the use of aMRI for patients with VIS-C seems to be the most cost-effective strategy for HCC screening in patients with NAFLD cirrhosis.[6] It would be of great importance to compare NC-MRI vs US imaging alone (VIS-A) or the US VIS-based approach (VIS-B or VIS-C) for HCC surveillance.

Rhee et al[1] provide compelling evidence supporting NC-MRI as a promising HCC surveillance tool. Further research integrating cost-effectiveness analyses and US VIS will refine its role in clinical practice. We commend the authors for advancing this critical field and look forward to future studies optimizing surveillance paradigms for at-risk populations.

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Assessing the Diagnostic Performance of Renal Ultrasound in Microhematuria Evaluation: Validation of the AUA Microhematuria 2020 Guidelines

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diagnosed on CT were missed on concurrent ultrasound (1.2%). In patients with a negative ultrasound during initial workup with follow-up cross-sectional imaging between 2018 and 2023 (n=401), 3 kidney cancers were diagnosed on subsequent imaging (0.75%). Median time to subsequent diagnosis was 398 days and all masses were cT1.

Conclusion

In a large microhematuria population, renal ultrasound was frequently performed during initial workup with a rare missed or subsequent cancer diagnosis rate. Subsequent imaging after RUS was typically prompted by the development of symptoms, but follow-up studies showed early-stage disease, suggesting diagnosis was made in a timely fashion.

CLINICAL NEWS | WOMENS IMAGING

False-negative breast exams on the rise

Amerigo Allegretto

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False-Negative Screening and Diagnostic Mammograms in the National Mammography Database From 2010 to 2022

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was lower for race categories other than White (OR=0.30-0.95), higher for breast density categories other than almost entirely fatty breasts (OR=1.60-2.00), higher for women with personal (OR=3.69) or family (OR=1.29) history of breast cancer, and higher for academic or university-based facilities (OR=1.37); for diagnostic examinations, the likelihood of a FN examination was lower for race categories of Asian (OR=0.91) and Hawaiian (OR=0.77) and higher for a race category of Black (OR=1.12), lower for Hispanic patients (OR=0.70), higher for heterogeneously (OR=1.46) or extremely (OR=1.86) dense breasts, higher for women with personal (OR=7.82) or family (OR=1.31) history of breast cancer, and higher for academic or university-based facilities (OR=1.37).

Conclusion: Rates of FN screening and diagnostic mammograms increased over time and showed significant associations with patient and facility characteristics.

Clinical Impact: Exploration of the causes of the observed associations could inform quality assurance efforts to reduce the risk of delayed breast cancer diagnoses.

THE END