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Enteron

Dear Doctor,

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Best Regards,
Medical Team, Micro Labs Ltd

Novel antisense drug in NAFLD

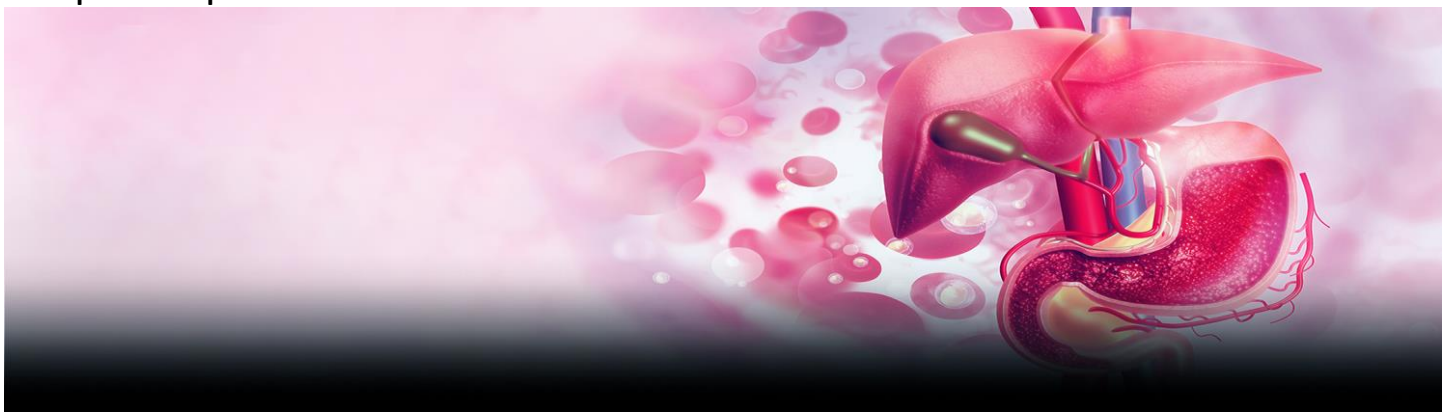
Using a first-of-its-class drug in a clinical trial, an international research effort headed by a scientist at University of California San Diego School of Medicine reports that inhibition of a key enzyme safely and effectively improved the health of persons with non-alcoholic fatty liver disease (NAFLD), a chronic metabolic disorder that affects hundreds of millions of people worldwide.

The gene silencing approach represents a novel way to reverse NAFLD. The findings are published in the June 15, 2020 online issue of The Lancet Gastroenterology and Hepatology.

NAFLD occurs when fat accumulates in liver cells due to causes other than excessive alcohol intake. The precise cause is not known, but diet and genetics are believed to play substantial roles. The condition is typically not noticed until the disease is well-advanced, and perhaps has transitioned to non-alcoholic steatohepatitis (NASH), a progressive form that can lead to cirrhosis, liver cancer and liver failure.

There is no cure. Treatment primarily consists of ameliorating contributory factors, such as losing weight, improving diet, exercising more and controlling for other conditions, such as diabetes and hypertension. No Food and Drug Administration-approved medications exist. In worst cases, a liver transplant may be required.

In the double-blind, randomized, placebo-controlled Phase II trial, Loomba and colleagues enrolled 44 qualifying participants at 16 sites in Canada, Poland and Hungary. For 13 weeks, participants were injected with either an antisense inhibitor called IONIS-DGAT2 or a placebo. The inhibitor, produced by Carlsbad-based Ionis Pharmaceuticals, interferes with Diacylglycerol-O-acyltransferace or DGAT2, one of two enzyme forms required to catalyze or accelerate the production of triglycerides, a type of fat found in blood. High levels of triglycerides boost fat storage throughout the body, including the liver.

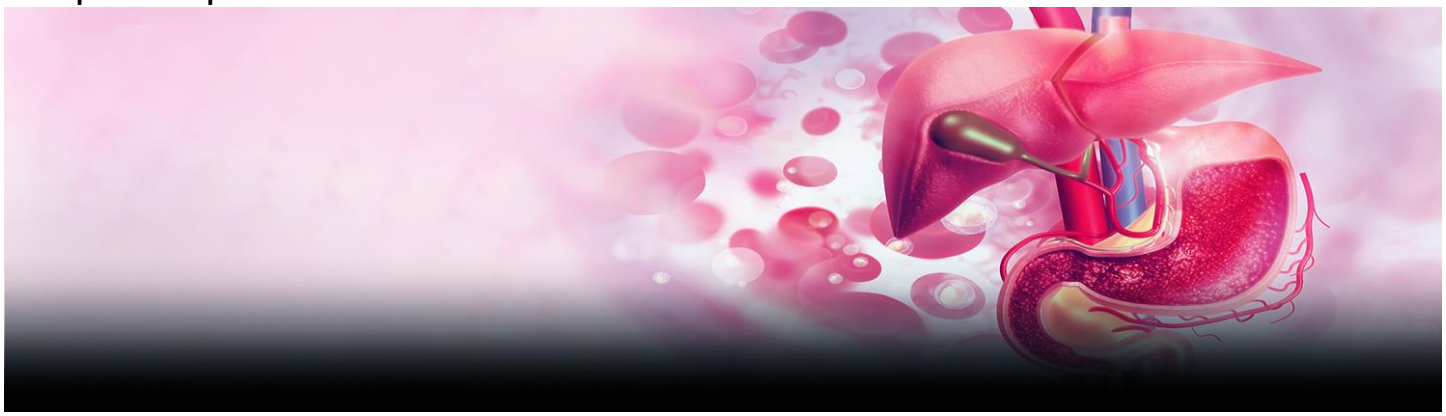


The researchers found that after 13 weeks of treatment, participants who received the enzyme inhibitor experienced measurable reductions in fatty liver levels compared to baseline, without elevated levels of fats, enzymes or sugars in the blood. There were six reported serious adverse events, including a cardiac arrest and deep vein thrombosis, but the researchers determined the events were unrelated to the study drug.

Loomba said that these findings showed robust reduction in liver fat by MRI without corresponding increases in blood lipids. Given significant proportion of patients achieving roughly a 30 percent reduction in MRI-PDFF, the threshold that corresponds with higher odds of histologic response when treated for a longer duration, it looks like after just 13 weeks of treatment, the drug was actually slowing progression of NAFLD to NASH.

All of this is very encouraging and argues for the next step: longer term trials to further investigate the potential of this drug in improvement of liver histologic features associated with NASH, the progressive sub-type of NAFLD.

Source: Loomba R, et al. Novel antisense inhibition of diacylglycerol O-acyltransferase 2 for treatment of non-alcoholic fatty liver disease: a multicentre, double-blind, randomised, placebo-controlled phase 2 trial. The Lancet Gastroenterology and Hepatology. 2020; doi.org/10.1016/S2468-1253(20)30186-2.



Treatment of Previously Treated HER2-Positive Gastric Cancer with Trastuzumab Deruxtecan

INTRODUCTION

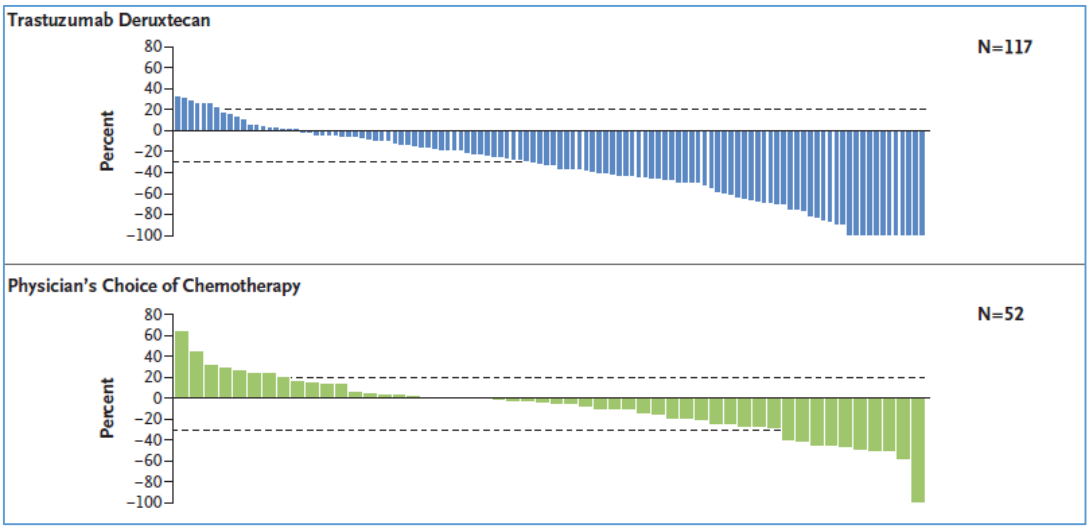
An estimated 15 to 20% of advanced gastric and gastroesophageal junction cancers, which are especially prevalent in East Asia, have overexpression or amplification of human epidermal growth factor receptor 2 (HER2). Chemotherapy plus the anti-HER2 antibody trastuzumab is the recommended firstline therapy on the basis of the randomized, multicenter, phase 3 ToGA (Trastuzumab for Gastric Cancer) trial, in which overall survival was significantly longer with chemotherapy plus trastuzumab than with chemotherapy alone (median, 13.8 months vs. 11.1 months). Regardless of HER2 expression, paclitaxel plus ramucirumab (an anti–VEGFR-2 [vascular endothelial growth factor receptor 2] antibody) is recommended as second-line therapy and is associated with a median overall survival of 9.6 months (vs. 7.4 months with paclitaxel alone), with somewhat prolonged progression-free survival (median, 4.4 months vs. 2.9 months) and higher response (28% vs. 16% of the patients). For later lines of treatment, irinotecan, taxanes, trifluridine–tipiracil, and immune checkpoint inhibitors are additional options. As compared with placebo, nivolumab minimally prolonged overall survival (4.1 months vs. 5.3 months), as did trifluridine–tipiracil (3.6 months vs. 5.7 months). Furthermore, several HER2-targeting agents did not prolong overall survival in patients with gastric cancer. A recent phase 1 study assessed treatment treatment with trastuzumab deruxtecan at a dose of 5.4 mg or 6.4 mg per kilogram of body weight in 44 patients with HER2-positive gastric or gastroesophageal junction cancer who had been previously treated with trastuzumab. Positivity for HER2 was defined as a score of 3+ (positive) on immunohistochemical analysis or a score of 2+ (borderline) with positive results on in situ hybridization (such results are designated as high-level HER2 expression in this article). The objective response according to investigator assessment was 43.2%, the median duration of response was 7.0 months, and the median progression- free survival was 5.6 months. Among patients who had previously received irinotecan, a different topoisomerase I inhibitor, 41.7% had a response, which suggests minimal cross-resistance with the trastuzumab deruxtecan payload. Here, the authors share the results of an open-label, multicentre, phase 2 trial of trastuzumab deruxtecan in patients with HER2-expressing advanced gastric cancer or gastroesophageal junction adenocarcinoma that had progressed after the receipt of at least two previous therapies.

METHODS

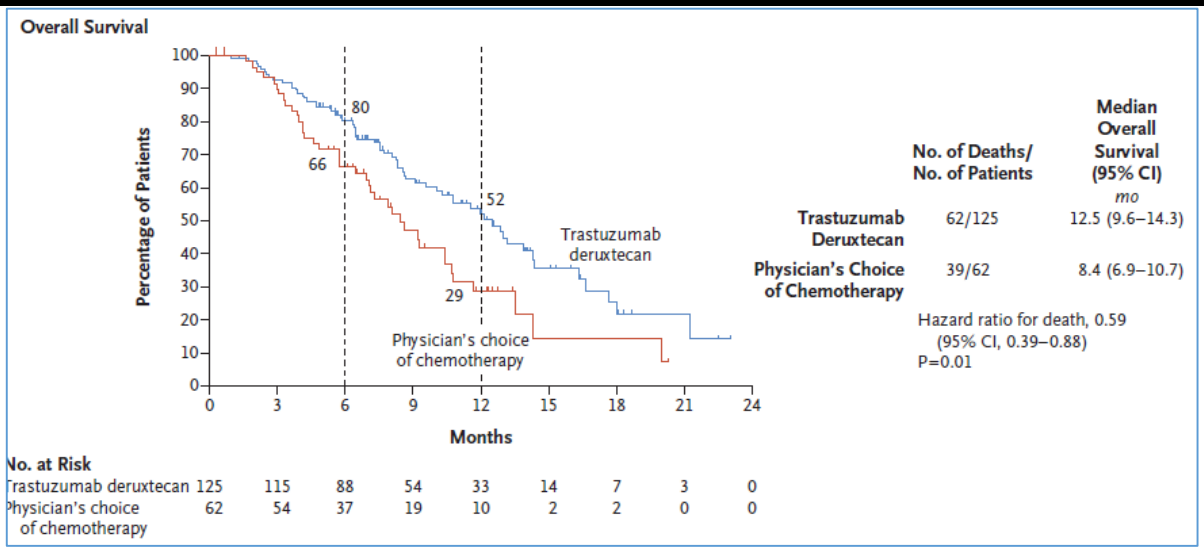
In an open-label, randomized, phase 2 trial, they evaluated trastuzumab deruxtecan as compared with chemotherapy in patients with HER2-positive advanced gastric cancer. Patients with centrally confirmed HER2-positive gastric or gastroesophageal junction adenocarcinoma that had progressed while they were receiving at least two previous therapies, including trastuzumab, were randomly assigned in a 2:1 ratio to receive trastuzumab deruxtecan (6.4 mg per kilogram of body weight every 3 weeks) or physician's choice of chemotherapy. The primary end point was the objective response, according to independent central review. Secondary end points included overall survival, response duration, progression-free survival, confirmed response (response persisting ≥4 weeks), and safety.

RESULTS

Of 187 treated patients, 125 received trastuzumab deruxtecan and 62 received chemotherapy (55 received irinotecan and 7 paclitaxel). An objective response was reported in 51% of the patients in the trastuzumab deruxtecan group, as compared with 14% of those in the physician's choice group (P<0.001). Overall survival was longer with trastuzumab deruxtecan than with chemotherapy (median, 12.5 vs. 8.4 months; hazard ratio for death, 0.59; 95% confidence interval, 0.39 to 0.88; P = 0.01, which crossed the prespecified O'Brien–Fleming boundary [0.0202 on the basis of number of deaths]). The most common adverse events of grade 3 or higher were a decreased neutrophil count (in 51% of the trastuzumab deruxtecan group and 24% of the physician's choice group), anemia (38% and 23%, respectively), and decreased white-cell count (21% and 11%). A total of 12 patients had trastuzumab deruxtecan– related interstitial lung disease or pneumonitis (grade 1 or 2 in 9 patients and grade 3 or 4 in 3), as adjudicated by an independent committee. One drug-related death (due to pneumonia) was noted in the trastuzumab deruxtecan group; no drugrelated deaths occurred in the physician's choice group.



Best Percentage Change from Baseline in the Sum of Longest Diameters of Measurable Tumors.



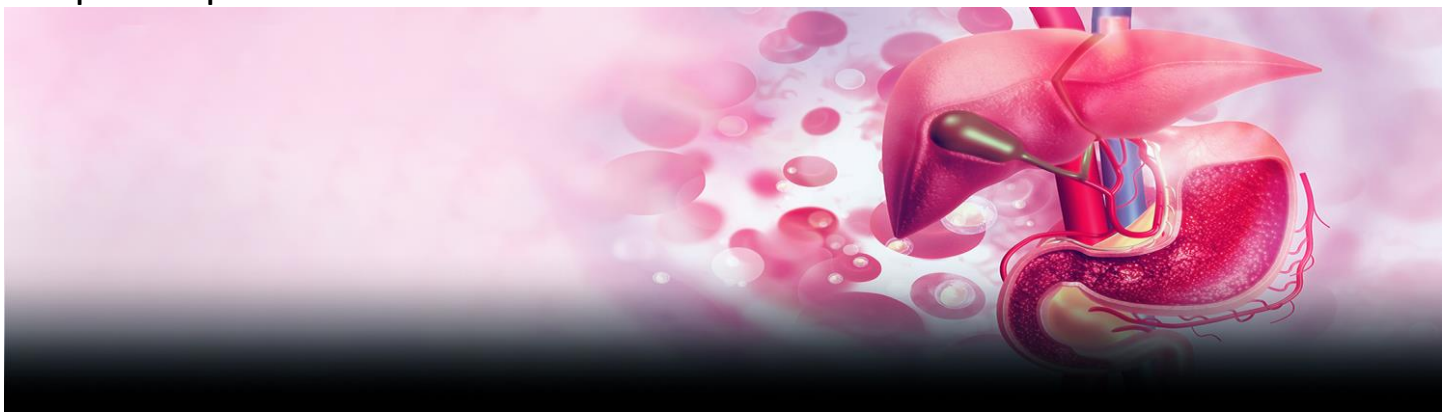
Overall Survival

CONCLUSION

Overall, treatment with trastuzumab deruxtecan led to a significantly higher percentage of patients with an objective response and to longer overall survival than conventional chemotherapy among patients with HER2-positive, advanced gastric or gastroesophageal junction cancer. Antitumor activity was noted in patients who had had disease progression while they had been receiving regimens including trastuzumab. Noteworthy toxic effects included myelosuppression and interstitial lung disease, which were ameliorated by dose reductions and interruptions.

REFERENCE

Shitara K, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Gastric Cancer. N Engl J Med 2020; 382:2419-2430



Acute Upper Gastrointestinal Bleeding: Timing of Endoscopy

INTRODUCTION

Acute upper gastrointestinal bleeding is one of the most common medical emergencies. A national audit from the United Kingdom estimated a crude overall inhospital mortality of 10% after acute upper gastrointestinal bleeding. Endoscopy allows identification of the source of bleeding, as well as hemostatic treatment for actively bleeding lesions. Endoscopic hemostatic treatment of high risk lesions stops bleeding and reduces the risk of further bleeding and the need for surgery. An international consensus group recommends endoscopy within 24 hours after presentation for patients with acute upper gastrointestinal bleeding. For patients who are at high risk for further bleeding or death, the consensus group could not make a recommendation for or against performing endoscopy within 12 hours as opposed to performing endoscopy later. Many observational studies, three randomized, controlled trials, and two systematic reviews have shown that urgent endoscopy (the definitions of which have varied among studies, ranging from within 2 hours to within 12 hours after presentation) in unselected patients with acute upper gastrointestinal bleeding did not decrease mortality. The three randomized trials were not designed to focus on patients at high risk for further bleeding or death and did not report an assessment of patients' risk. The Glasgow–Blatchford score is a validated risk-assessment score for the prediction of clinical outcomes, including the need for interventions and the risk of death (scores range from 0 to 23, with higher scores indicating a higher risk of further bleeding or death). In an international multicenter prospective study involving 3012 patients, a threshold score of 7 or higher was shown to provide the most accurate prediction of whether a patient will be determined to need endoscopic treatment. In the author's own validation study, a higher score was associated with a greater likelihood of undergoing endoscopic treatment, as well as with a higher risk of death.

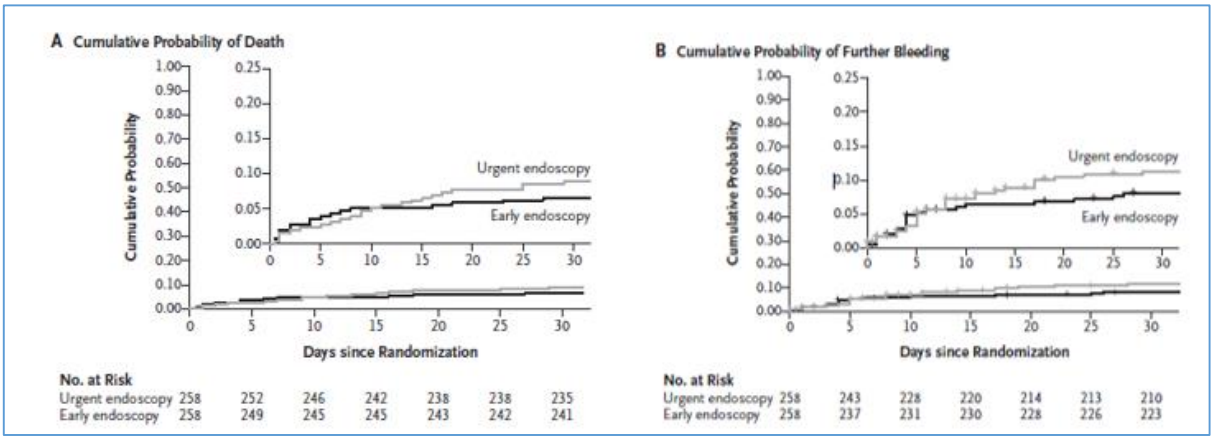
Recently, two large cohort studies provided conflicting results regarding the association between urgent endoscopy (within 6 hours after admission) and mortality. In a prospective cohort study involving 961 patients with Glasgow–Blatchford scores greater than 7, Cho et al. found that endoscopy performed within 6 hours, as compared with between 6 and 24 hours, was an independent predictor of lower mortality (odds ratio for death, 0.36; 95% confidence interval [CI], 0.14 to 0.95). However, in the study by Laursen et al., involving 2944 patients, the time frame for endoscopy that was associated with the lowest mortality was between 6 and 24 hours after admission. Mortality was higher among patients with hemodynamic instability or severe coexisting illnesses, defined as an American Society of Anesthesiologists grade of 3 to 5. A risk-assessment score was not used in that study. In this trial, the authors hypothesized that for patients with acute gastrointestinal bleeding who were predicted to be at high risk for further bleeding or death, endoscopy performed within 6 hours after gastroenterologic consultation would forestall further bleeding and improve outcomes as compared with endoscopy performed between 6 and 24 hours after consultation.

METHODS

To evaluate whether urgent endoscopy improves outcomes in patients predicted to be at high risk for further bleeding or death, patients were randomly assigned with overt signs of acute upper gastrointestinal bleeding and a Glasgow–Blatchford score of 12 or higher (scores range from 0 to 23, with higher scores indicating a higher risk of further bleeding or death) to undergo endoscopy within 6 hours (urgent-endoscopy group) or between 6 and 24 hours (early-endoscopy group) after gastroenterologic consultation. The primary end point was death from any cause within 30 days after randomization.

RESULTS

A total of 516 patients were enrolled. The 30-day mortality was 8.9% (23 of 258 patients) in the urgent-endoscopy group and 6.6% (17 of 258) in the early-endoscopy group (difference, 2.3 percentage points; 95% confidence interval [CI], −2.3 to 6.9). Further bleeding within 30 days occurred in 28 patients (10.9%) in the urgentendoscopy group and in 20 (7.8%) in the early-endoscopy group (difference, 3.1 percentage points; 95% CI, −1.9 to 8.1). Ulcers with active bleeding or visible vessels were found on initial endoscopy in 105 of the 158 patients (66.4%) with peptic ulcers in the urgent-endoscopy group and in 76 of 159 (47.8%) in the early-endoscopy group. Endoscopic hemostatic treatment was administered at initial endoscopy for 155 patients (60.1%) in the urgent-endoscopy group and for 125 (48.4%) in the early-endoscopy group.



Kaplan–Meier Estimates of the Cumulative Incidences of Death (A) and Further Bleeding (B).

CONCLUSION

In patients with acute upper gastrointestinal bleeding who were at high risk for further bleeding or death, endoscopy performed within 6 hours after gastroenterologic consultation was not associated with lower 30-day mortality than endoscopy performed between 6 and 24 hours after consultation.

REFERENCE

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