offered to HPS patients. In part this is because there are other recent fluxes in the prioritization of patients on the waiting list, not accounted for in this retrospective analysis. The introduction of the "share 35" regional sharing initiative is likely to raise the median MELD for acquisition of a deceased donor liver, and thereby ameliorate the advantage for HPS patients demonstrated in the present study.

The present study does point to a new PaO_2 category ($\leq$44 mmHg) with poor post-LT outcomes. It is notable that the only consideration about posttransplant outcomes in the "final rule" was in relation to futility, which is a high bar. There are no firm rules on what constitutes a futile transplant; colloquially, however, many transplant physicians refer to the guidance attributed to Dr Nancy Ascher of UCSF, that a LT is futile if the prognosis is that the graft has less than a 50% chance of surviving 5 years.[14] In Goldberg's study, even the worst outcomes do not reach that threshold of futility. We anticipate that individual centers will continue to incorporate anticipated post-LT mortality in their assessment of severely hypoxic candidates. The data in Goldberg's study may encourage some centers to reset their oxygenation threshold for post-LT outcome risk to include patients with a PaO_2 of $<$50 mmHg but $>$44 mmHg. Ultimately, the challenge to the transplant community is to find consensus on assessing priority on the LT waiting list across the spectrum of liver disease, at a time when donor organ allocation is a moving target. The study of Goldberg et al will be an essential reference in that ongoing reconsideration.

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Identifying Molecular Factors That Contribute to Resolution of Liver Fibrosis

See "Vascular endothelial growth factor promotes fibrosis resolution and repair in mice," by Yang L, Kwon J, Popov Y, et al, on page 1339.

The progression of liver fibrosis is a critical factor in patients with chronic liver diseases, because advanced fibrosis is a prerequisite to develop cirrhosis and its complications, and it predisposes patients to developing

hepatocellular carcinoma. Currently, the only effective approach to slow down the progression of fibrosis or even induce its regression is to remove the cause of the liver disease.[1] However, removal of the etiologic factor (ie, hepatitis B virus or hepatitis C virus clearance, alcohol cessation, weight loss) is not always possible and these patients would also benefit from antifibrotic therapies capable of attenuating the deposition of scar tissue in the liver. Additionally, patients with advanced fibrosis in whom the cause of the liver disease is removed (eg, a patient with alcoholic cirrhosis who stops drinking) would benefit from targeted therapies that favor fibrosis resolution and restoration of a normal liver architecture. To develop such drugs, it is essential to identify the main cellular and molecular mechanisms that mediate fibrosis resolution. Because liver tissue from patients with active fibrosis resolution is not routinely obtained for clinical practice and research purposes, experimental studies in animals with ongoing hepatic tissue repair seem appropriate to identify the molecular drivers of fibrosis resolution.

To understand its resolution, it is valuable to consider established hepatic fibrosis conceptually as having 3 components: The pathologic matrix, predominantly fibrillar collagens (collagens types I and III); the fibrogenic cell or myofibroblast (the source of both the matrix and the tissue inhibitors and metalloproteinases); and the cells that regulate matrix degradation, via secretion of matrix degrading metalloproteinase (MMPs).[2,3] Each of these components potentially represents a therapeutic target. Accumulating evidence now suggests that the cells contributing to the third component, a critical source of MMPs for matrix degradation in fibrosis resolution, are monocyte-derived macrophages recruited to the liver during the inflammatory phase of injury. Furthermore, these cells populate the liver in apposition and sometimes within the hepatic matrix, so-called scar-associated macrophages (SAMs). Moreover, to degrade fibrillar matrix it is axiomatic that the MMPs derived from these SAMS must have true collagenase activity (MMP1 in the human and MMP13 in the rodent). The recruitment and function of this population are a major focus of the elegant studies presented by Yang et al in this issue of *Gastroenterology*.[4]

For architectural remodeling to occur, the balance between the factors promoting matrix accumulation (synthesis of matrix by fibrogenic factors) and remodeling (matrix breakdown mediated by MMPs) needs to alter, shifting from one that favors matrix accumulation to one of net matrix degradation. Detailed studies of rodent models have shown that cessation of injury, whether by bilioduodenal anastomosis in chronic bile duct ligation or cessation of prolonged carbon tetrachloride, results in a shift in the balance of matrix synthesis and turnover, which is characterized by apoptosis of myofibroblasts, a reduction in the hepatic tissue inhibitors and metalloproteinase levels and the production of MMPs by resident and incoming cells.[3] Interestingly, studies of human liver biopsy samples, largely in the context of antiviral treatment, show parallel processes at play.[5] In the longer term and associated with functional recovery architectural restoration is required with a normal organ structure and repopulation with non-pathologic cell lineages (and phenotypes).[6]

A crucial finding in rodent models of advanced fibrosis is that the persistent scar tissue contains not only fibrillar collagen, but is also rich in elastin (a matrix protein only susceptible to degradation by specific elastases such as MMP12). Additionally, scar tissue contains monocyte-derived macrophages, which are associated with fibrogenesis. These monocyte-derived macrophages are a potent source of a range of MMPs, including collagenases such as MMP13, able to make the first cleavage of native collagen, gelatinases (MMPs 2 and 9) able to fully degrade partially denatured collagen following the action of collagenases, and elastases including the potent macrophage metalloelastase, MMP12.[4,7,8] Work by a number of groups, including the study by Yang et al in this issue of *Gastroenterology*, has demonstrated that macrophages are crucial to the resolution of fibrosis.[4,7,9–11] Indeed, the removal of the macrophage population at the onset of spontaneous fibrosis resolution in rodent models of liver injury prevents remodeling of fibrosis. Additionally, deletion of the macrophage population is associated with a critical drop in liver levels of key enzymes such as MMP13 and MMP12—identifying the macrophage as a crucial source of these enzymes in fibrosis resolution. Intriguingly, in the carbon tetrachloride-induced model of liver injury, the macrophages crucial for resolution are the same population that is recruited during fibrogenesis, and that contribute to fibrosis.[9,10] Associated with the onset of fibrosis resolution, this same macrophage population undergoes a phenotypic switch in situ, expressing markers that define a distinct phenotype and up-regulate the expression of matrix-degrading enzymes (and survival and proliferative signals for hepatocytes and hepatic progenitor cells) after ingestion of debris.[6,10]

Against this background, the work by Yang et al[4] provides another crucial insight to the molecular regulators of fibrosis resolution. As identified by the authors, vascular endothelial growth factor (VEGF) has previously been found to play a role in fibrogenesis via a pro-inflammatory effect acting primarily on endothelial cells. The inhibition of VEGF function in progressive fibrosis, therefore, theoretically represents an attractive therapeutic target. However, aware of the dichotomous role played by specific mediators such as macrophages in fibrosis and fibrosis resolution, Yang et al[4] have undertaken detailed studies of the inhibition of VEGF in models of fibrosis resolution. Their data indicate that VEGF does indeed play a dual role in fibrosis and fibrosis resolution (Figure 1). VEGF inhibition in the resolution phase is associated not with a beneficial effect, but with a failure of matrix remodeling. Moreover, their data show that although there was no evidence of differential neutrophil migration with and without VEGF neutralization, there was a clear association with a reduced number of SAM in the absence of VEGF signaling. The authors present data indicating that VEGF promotes sinusoidal permeability, monocyte-endothelial cell adhesion, and the resulting SAM accumulation necessary for fibrosis resolution. These data also confirm a crucial role for SAM in the resolution of bile duct ligation–induced fibrosis, to complement the existing and growing literature showing the importance of these cells in parenchymal (CCl_4- and dietary-induced) models of fibrosis.