Fibrosis as an End Point for Clinical Trials in Liver Disease: A Report of the International Fibrosis Group

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Deaths due to the consequences of advanced liver fibrosis and cirrhosis remain a significant cause of mortality worldwide. Biologically plausible pathways involved in hepatic fibrogenesis have also led to the identification of numerous preclinical and clinical compounds that have received great interest as potential future therapeutic agents for patients with liver fibrosis. With this in mind, stake holders from academia, regulatory agencies, clinicians, and the pharmaceutical industry met to understand and discuss the many complex issues involved in developing potential therapeutic agents which act primarily through modifying fibrosis and to discuss appropriate end points for clinical trials in these patient populations. In this article, we summarize those discussions and attempt to highlight many of the hurdles and unanswered questions as we attempt to move forward and develop therapies to combat liver fibrosis.

Globally, liver fibrosis and cirrhosis lead to 1.4 million deaths annually. The development of antifibrotic therapies has been hampered by an inability to define acceptable clinical end points within a reasonable period of study. The various end points proposed include hepatic imaging, biological or serum markers of inflammation and hepatic fibrosis, and liver biopsy examination. A critical evaluation of the relative merits and drawbacks of these potential end point measurements has not been performed.

On February 3 and 4, 2005, representatives from leading academic medical centers, government agencies, and the pharmaceutical and biotechnology industries met to discuss fibrosis as an end point in clinical trials involving patients with liver disease. The focus of the meeting was a critical appraisal of current potential end points and recommendations for future research and regulatory directions.

Background and Rationale for Antifibrotic Therapy

Liver fibrosis results from excessive extracellular matrix deposition in the liver in response to persistent viral, toxic, or immunologic injury. Hepatic fibrosis is determined by the balance between fibrogenesis and fibrosis regression (fibrolysis). When this balance favors fibrogenesis, there is an accumulation of collagen and extracellular matrix that eventually leads to cirrhosis. The optimal antifibrotic therapy is treatment or removal of the profibrogenic stimulus. There are now multiple studies, case series, and case reports in which fibrosis and even cirrhosis have been reversed after patients with viral- and autoimmune-associated liver injury were treated successfully for their primary disease.[1-6]

The majority of patients with chronic liver disease do not respond in such a dramatic fashion to treatment of the underlying disease. In particular, treatment is either ineffective or unproven for many patients with the 2 most common liver diseases in the United States: chronic hepatitis C virus (HCV) infection and nonalcoholic steatohepatitis (NASH). Therefore, for many patients effective antifibrotic agents are a clinically meaningful and important strategy for preventing and treating cirrhosis, and potentially preventing clinical complications of advanced liver disease.

Yet there are specific difficulties in developing and evaluating antifibrotic agents. The purpose of our meeting—and therefore this report—was to discuss such challenges and methods of working through them to move the process of development forward.

Mechanisms of Hepatic Fibrosis and Targets for Therapy

Hepatic fibrosis represents the liver's response to injury. The mechanisms underlying the fibrogenic response have been under intense investigation for the past 2 decades, and this research has helped elucidate the cellular mechanisms for the healing response to liver injury. The data indicate that the wounding response is linked to transformation of resident stellate cells (also known as *lipocytes*, or *perisinusoidal cells*) from a quiescent state (found in the normal liver) to an activated state (found in the injured liver). The transformation results in a prominent increase in secretion of extracellular matrix proteins such as collagen (types I, III, IV, and others) and various forms of fibronectin, laminin, and proteoglycans. Evidence indicates that the extracellular matrix proteins produced by stellate cells closely parallel those identified in the whole liver.[7]

Mechanisms underlying stellate-cell activation are complex; many important pathways have been identified.[8] Further, activation leads to a multitude of phenotypic effects, such as fibrogenesis, proliferation, chemotaxis, contractility, and even matrix degradation—all important in the response to injury (Figure 1).[9] Many of these pathways of stellate-cell activation are potential targets for treatment. Indeed, the advances in

Abbreviations used in this paper: AUROC, area under the receiver-operator characteristic curve; HCV, hepatitis C virus; NASH, nonalcoholic steatohepatitis.

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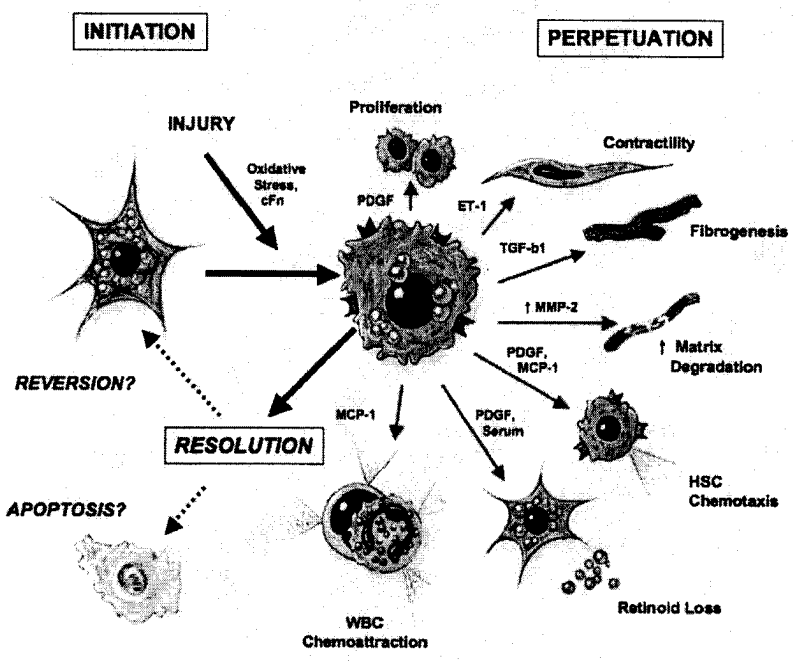

Figure 1. The hepatic stellate cell, in response to injury, is activated to initiate and subsequently perpetuate a series of events as shown. Activation of stellate cells results in changes in function and form, as depicted, that lead to the development of a profibrotic state. Such changes include stellate-cell proliferation, increased contractility, intracellular retinoid loss, enhanced fibrogenesis, matrix degradation, chemotaxis, and white blood cell (WBC) chemoattraction. Some, or all, of these pathways theoretically could be targeted to develop potential therapeutic agents that may interrupt, reverse, or abrogate intrahepatic fibrogenesis. PDGF, platelet-derived growth factor; ET-1, endothelin-1; TGF-B1, transforming growth factor b1; MMP-2, matrix metalloproteinase-2; MCP-1, monocyte chemotactic protein 1. Adapted and reprinted with permission from Friedman.[9]

understanding the molecular pathways involved in fibrogenesis have led to multiple novel proposed antifibrotic therapies (Table 1). Although a rationale exists for the use of each agent individually, many experts believe that the reversal of such a complex process as fibrosis will require treatments that target multiple pathways. Many of the proposed treatments have approved indications for other diseases but have not been evaluated in registration-quality trials for liver fibrosis. The development of these new therapies, either as monotherapies or combination therapies, will require close collaboration between basic scientists, clinical researchers, biopharmaceutical companies, and regulatory authorities.

Barriers to Developing Antifibrotic Agents

We focused on the concepts of general hepatic antifibrotic agents rather than specific therapies aimed at the underlying primary disease process. The assumption is that true antifibrotic agents will have efficacy across a wide range of liver diseases, regardless of the primary insult, because they focus on the primary process of fibrogenesis: inadequate and inappropriate repair. Although several potential agents for inhibiting fibrosis exist (Table 1), there are barriers to their development that may make investment by pharmaceutical companies less appealing from a cost/benefit standpoint.

The first barrier is the relatively slow or uncertain natural history of fibrosis progression for the majority of liver diseases, in particular for NASH and HCV, which evolve over decades.

Table 1. Experimental Antifibrotic Agents

5-lipooxygenase inhibition,[a] 5-lipoxygenase-activating protein inhibitors[a]	Interferon-γ, -alfa
AA861	Mycophenolate
Angiotensin-converting enzyme inhibitors	Octreotide[a]
Anti-a1 integrin[a]	Pentoxifylline
Arginine-glycine-aspartate peptides	Phosphatidylcholine[a]
Caspase inhibitors[a]	Peroxisome proliferator-activated receptor ligands
Estradiol[a]	Prostaglandins, prostaglandin E2
Endothelin A receptor antagonists	Quercetin[a]
Farnesoid X receptor agonists	Rapamycin
Glycyrrhizin[a]/*Salvia miltiorrhiza*[a]	Retinoic acid
Halofuginone	Sho-saiko-to (TJ-9)
Hepatocyte growth factor[a]	Soluble platelet-derived growth factor antagonists
High-dose anti-oxidants (Silymarin)	Soluble type II fusion molecule
HOE 77[a]	Transforming growth factor B-receptor blockade
Interleukin-1 antagonists[a]	

[a]There are no data to clearly indicate antifibrotic effects in suitable animal models or cell culture models for the indicated agents. Some of these agents may have anti-inflammatory effects that, in theory, could retard or prevent the development of fibrosis by suppressing the inflammatory response, or alternatively have been reported to have an antifibrotic effect in certain systems.

Second, evaluating the pharmacokinetics and pharmacodynamics of these compounds and relating them to intrahepatic antifibrotic efficacy remains challenging. Reliable end points and surrogate markers are needed to ensure potential antifibrotic drugs target the liver preferentially and produce clinically meaningful benefits. To justify the high costs of early clinical development, reliable and reproducible short-term end points acceptable to both industry and regulatory authorities are required to provide a go/no-go decision point for further study.

Well-characterized, homogeneous populations are preferred for early efficacy trials to decrease variability in response rates across different disease stages, and to best provide pharmacokinetic and pharmacodynamic data for the most appropriate dose selection. Even studies in homogeneous populations may require large sample sizes to detect these effects.

In addition, study end points sometimes change from initial proof-of-concept studies, in which evidence of biological activity of a therapeutic agent is of primary importance, to larger registration trials, in which change in fibrosis on liver biopsy examination or clinical end points are of primary importance. Measuring biochemical markers in serum would be less invasive and potentially less costly and more convenient than liver biopsy examination, but currently biopsy examination is the standard used to measure treatment efficacy. Once there are biomarkers that correlate with biopsy examination findings, however, larger efficacy trials could be undertaken with some confidence using these biomarkers. Clinical end points such as death, transplantation, variceal hemorrhage, other clinical decompensations, or hepatocellular carcinoma would be more objective and meaningful measures of efficacy, but their measurement requires very large sample sizes and a long follow-up period. Future development of antifibrotic therapies will require active collaboration between the pharmaceutical industry and regulatory authorities to define appropriate target populations, relevant end points, and acceptable safety profiles.

Limitations of Liver Biopsy Examination as a Clinical End Point

Because fibrosis is defined by morphologic criteria, a biopsy examination would seem to be the optimal method to evaluate change in fibrosis over time. Biopsy examinations have indeed been used to assess the performance of biomarkers and other surrogate end points, yet the use of liver biopsy examination for these purposes has several important limitations.

Needle biopsy examination samples only 1/25,000-50,000 of the liver and for many reasons are prone to sampling error. In addition to sampling size, the heterogenous nature of liver fibrosis leads to incorrect staging of hepatic fibrosis in 10%-30% of patients.[10]

Another drawback to using biopsy specimens is that staging can vary as much as 62% between observers.[10-13] In 1 study, even when biopsy samples were larger than 10 mm, variation remained as the samples increased in length.[14] In addition, the technique used and the size and type of needle can greatly influence disease scoring, even under the standardized requirements of trial protocols. A liver biopsy examination is also an invasive procedure that carries finite risks of morbidity and mortality. For this and other reasons, at least 10% of trial participants typically do not undergo a follow-up or second biopsy examination as required in study protocols. Accounting for these missing data results in an increase in trial sample sizes, and therefore increases costs. However, perhaps the most serious limitation of biopsy examination as an end point is that it is a static measurement of fibrosis and does not reflect the dynamics of the disease process. An effective agent could retard fibrogenesis significantly or promote fibrosis regression but appear ineffective using standard histology. In an attempt to better quantify these changes, computer-assisted image analysis to quantitate fibrosis and special stains to evaluate stellate-cell activation have all been proposed, but not yet validated in clinical trials.

Very few studies have assessed the ability of 1 biopsy sample, or serial biopsy samples, to predict clinical end points such as death or transplantation. In a large study of serial biopsy specimens from patients with primary biliary cirrhosis, those with cirrhosis at baseline had a 15-year mortality rate of approximately 15%, whereas those with portal fibrosis showed only minimally decreased survival.[15] In another study, baseline histology correlated with mortality over a mean follow-up period of 6.9 years.[16] Similar patterns were seen in studies performed in the 1970s of hepatitis B virus patients with chronic persistent or active hepatitis and cirrhosis.

When planning a registration study of an antifibrotic agent, biopsy examinations should be repeated when a statistically and clinically significant difference in fibrosis progression is likely to be detected between the study arms. The definition of clinically significant improvement will vary by disease state, desired study power (including confidence intervals), intended treatment effect (stabilization vs regression), and anticipated magnitude of treatment effects.

Unfortunately, there is little available information to guide trial and end point design about the optimal interval between biopsy examinations. For chronic, slowly progressive diseases, biopsy examinations often are performed at 12- to 24-month intervals; for more rapidly progressive diseases the interval is often 6-12 months. For pilot efficacy studies, an interval of 12-24 months might seem adequate. For confirmatory efficacy studies that have fibrosis as a primary outcome, it seems reasonable to use the same intervals as in the earlier studies in a specific disease state, allowing for subsequent meta-analyses and other comparisons. In initial studies aimed at correlating biopsy examination results with new biomarkers, biopsy samples might need to be obtained more often, possibly every 3-6 months. Such studies should be designed with the shortest possible duration to limit the number of times patients undergo repeat liver biopsy examination.

Compared with most diagnostic tests, very few data exist regarding the sensitivity, specificity, positive and negative predictive values, and discriminatory ability of liver biopsy examinations in various disease states. For initial proof-of-concept studies, it may be more efficient to use pharmacodynamic or other surrogate markers of effect, reserving biopsy examinations (at a predetermined interval) for larger efficacy and outcomes studies.

Surrogate Biomarkers as an Alternative to Biopsy Examination in Fibrosis Clinical Trials

In evaluating the diagnostic ability of liver-related biomarkers, investigators have used the area under receiver-operator characteristic curve (AUROC), sensitivity, specificity, positive and negative predictive values, likelihood ratios, and

accuracy. In the end, it is the clinical usefulness of the marker that is most important. A clinically useful biomarker must have acceptable error rates and be compared easily with alternative tests in practical terms.

In a recent analysis of 10 validated sets of biomarkers that distinguished insignificant vs significant fibrosis in patients with HCV infection, a test was categorized arbitrarily as correct when the true-positive and true-negative rates reached a given threshold.[17] A correct result was determined by the true-negative rates; that is, if test performance allowed assignment of approximately a 95% sensitivity or 90% specificity.

Most marker panels showed similar predictive ability: the AUROC values all were approximately .8. These tests were slightly better at discriminating patients with cirrhosis than those with lesser degrees of fibrosis. Most panels also performed well when the threshold for specificity was set high or low[17]: if the threshold was set high, the true-positive rate was high, and the true-negative and false-positive rates were acceptable. For a very low threshold of specificity, the true-negative rate was very good and the false-negative rate was acceptable. The negative predictive value was approximately 95%, and the positive predictive value was approximately 90%.

However, if the specificity threshold was in the midrange, panels determined the presence or absence of significant fibrosis in only approximately 40% of patients. Nearly all of these studies have focused on the single cross-sectional diagnosis of liver fibrosis for which they all have similar performance characteristics. For clinical trials, serial data reflecting fibrosis over time are required. Data from 2 studies that examined the correlation between a panel of 6 biomarkers and biopsy examination results from trial participants with HCV infection suggested that the panel could be used to guide evaluation and follow-up evaluation.[18,19]

A significant confounding factor is that biopsy examination has been used as the gold standard for validation studies of biomarkers but biopsy examination itself is prone to staging error. In one prospective study the frequency and causes of discordance between biopsy examination results and biomarker panels were examined in 537 patients with HCV infection.[20] Fibrosis stage and activity grade were assessed on the same day by biopsy examination first and then the FibroTest and ActiTest panels. The overall rate of discordance was 29%, including 16% for fibrosis staging and 17% for activity grading. Biopsy examination failure was more frequent than marker failure (18% vs 2.4% of cases, respectively) and most often consisted of false negatives in activity grading and fibrosis staging. Steatosis, inflammation, and smaller biopsy specimens all correlated with discordance. Interestingly, recent data also have suggested that biomarkers such as the FibroTest and YKL-40 also can have a significant predictive value for clinical outcomes.[21] FibroTest was more sensitive than biopsy examination in predicting liver-related mortality in a large group of HCV patients, and YKL-40 has been shown to predict mortality in alcohol-related liver diseases.

Noninvasive hepatic imaging represents another modality that needs to be validated further and incorporated into clinical trials. One such example is transient elastography (FibroScan; Echosens Co., Paris, France), a recently reported, noninvasive, rapid bedside method of assessing fibrosis by measuring liver stiffness.[22] In a prospective study of 183 patients with chronic HCV infection, AUROC values for the FibroScan, FibroTest, and aspartate aminotransferase-to-platelets ratio index were similarly high. Combining the FibroScan and FibroTest findings yielded the best result (AUROC .88 for F $\geq$ 2 disease). When the FibroScan and FibroTest results agreed, biopsy examination results confirmed these findings in the majority of patients. The combined use of FibroScan and FibroTest or other future biomarkers could greatly reduce the need for biopsy examinations.

Table 2. Potential Biomarkers of Hepatic Fibrosis

Immunohistochemical markers	Genetic/serum markers
Basement membrane constituents	Angiotensin (-2) pathways
C-terminal procollagen α1(III) propeptide	DDX-5
Cytoskeletal proteins	Glutathione S-transferase pi
Desmin	Interferon-γ
Neuroproteins	Interleukin-10
Smooth muscle α-actin	Leptin
Extra domain-A fibronectin	Matrix metalloproteinase 3
Fibrillar collagens	Telomerase
Glial fibrillary acidic protein	T-GEP
Growth factors	TIP-1
Laminin	Transforming growth factor β1

NOTE. Many of these genetic markers have been evaluated only in single studies in certain liver diseases or are theoretic at this stage. They have not necessarily been confirmed in other liver diseases and at best may predict risk in an already diseased group. As such, the field of biomarker development to predict fibrosis and disease outcome or treatment response is in the early stage of development and exploration. Apart from current existing biomarker panels as described in the text, further work is required in these areas.
DDX-5, DEAD (Asp-Glu-Ala-Asp) box polypeptide 5.

Immunohistologic markers also have been proposed as substitutes for traditional histologic interpretation of liver biopsy examination (Table 2).[23-26] Of these, smooth muscle α-actin, which is correlated inversely with the success of antiviral treatment of HCV and hepatitis B virus infection, has shown the most promise.[27] However, these measures still require liver sampling, and none has been reproduced or correlated consistently with other fibrosis measures. The real value of this type of immunohistochemistry may be to provide an early signal in phase 2 trials that a potential antifibrotic drug is resulting in the intended biological activity.

The evaluation of genetic markers of fibrosis has at least 2 current limitations (Table 2). First, large, definitive studies have not been completed, although they have been reported in abstract form.[28] Second, gene products reflect the possible risk, not manifestation or degree, of the disease. Gene polymorphisms have been examined, but most studies have been very small, performed at single centers, and limited by referral bias. The importance of identifying such markers may be to target particular subpopulations of patients in clinical trials that have a higher propensity to develop more advanced or rapidly progressive fibrosis, ultimately enabling faster trials that require fewer patients.

Clearly, evidence-based data will be required for biomarkers to be considered as true surrogates for liver fibrosis. Current biomarkers should show that they reflect not only the stage of fibrosis, but be dynamic inasmuch as changes in the surrogate would indicate either progression or regression of disease and

correlate to the clinical outcomes associated with liver fibrosis. Validating biomarkers generally involves dividing patients into 1 of 2 categories, such as cirrhosis or not cirrhosis, but defining and validating relative changes in biomarkers could be useful in evaluating treatment responses, especially in short-term trials.

The lack of biomarkers for fibrosis has been recognized as a research priority for the National Institutes of Health.[29] Biomarkers that could be used as surrogate markers for cirrhosis include those that have been observed in prospective studies as having AUROCs greater than .85 for cirrhosis stage correlated with fibrosis progression or regression. Before tests are used as surrogate markers of minimal or intermediate fibrosis, prospective studies should validate their prognostic value with strong clinical end points and survival.

Regulatory Issues Regarding Antifibrotic Therapies

At present there are no regulatory guidelines that clearly articulate the evidence required for approval of a pharmacologic treatment for liver fibrosis. This substantially increases the financial risk that pharmaceutical companies have in developing new agents. Establishing consensus standards for regulatory reviewers and industry would significantly facilitate development of potential new treatment options.

The ideal path for developing a new antifibrotic would start with an in-depth, detailed understanding of its biological mechanism of action and potential therapeutic benefit.

Although the prognostic value, accuracy, precision, and reproducibility of surrogate biomarkers need to be evaluated, given the unmet medical needs and health consequences of liver fibrosis, regulatory authorities should look favorably on the use of a validated surrogate as a primary end point. However, before this approach can be applied consistently, the degree of validation needed from prospective clinical trials needs to be established.

The US Food and Drug Administration's Critical Path Initiative[30] describes the need for the US Food and Drug Administration, together with academia, patient groups, industry, and other government agencies, to "embark on an aggressive, collaborative research effort to create a new generation of performance standards and predictive tools that will provide better answers about the safety and effectiveness of investigational products, faster and with more certainty." Such an approach is needed to speed therapeutic advances for treating liver fibrosis. Accepted standards for measuring clinical benefit must be established within the context of benefit-risk assessments, leading to marketing approval of promising new effective and safe treatments for liver fibrosis.

In the United States, there are a number of regulatory mechanisms designed specifically to address unmet medical needs and expedite the availability of new drugs intended to treat diseases that are serious and life-threatening.[31,32] Importantly, a well-established mechanism exists that allows initial product approval based on the effect of a drug on a surrogate end point that is reasonably likely to predict clinical benefit.[33] Data to support such an approach can be derived from epidemiologic, therapeutic, pathophysiologic, or other evidence. These mechanisms should be an integral part of new regulatory guidelines.

Appropriate risk-benefit assessments are critical before and after approval of new treatments. If an agent is very safe and well tolerated, a smaller treatment effect might be acceptable. For advanced disease or critical conditions for which effective therapies are lacking, more risk would be acceptable, given the potential for benefit. The magnitude of benefit also impacts the acceptable population exposure requirements to support initial marketing and evidentiary standards for independent substantiation of experimental results.

As noted earlier, there is an urgent need to identify new biomarkers that predict clinical benefit of antifibrotic agents. A potential critical step in the regulatory pathway would be acceptance of cirrhosis as both a histologic and clinical outcome. There are several advantages to accepting cirrhosis as a clinically relevant end point. First, cirrhosis represents the fibrosis end point with which the risk of clinical outcomes such as liver failure and liver cancer are associated. Second, the diagnosis of cirrhosis by liver biopsy examination, biomarkers, and imaging is optimal compared with earlier stages of fibrosis. Finally, the progression of fibrosis from Ishak stages 3 and 4 to cirrhosis is relatively predictable and would be acceptable from the issues of both study design and study size.

Optimal Design of Antifibrotic Studies

The ideal pilot study of an antifibrotic would have 3 primary aims: (1) to include restricted populations in whom fibrosis or cirrhosis are very common, such as those with HCV or NASH; (2) to reproducibly detect changes in fibrosis and fibrogenesis; and (3) to develop an accurate, accepted, noninvasive test that correlates with changes in histologic fibrosis and fibrogenesis. These goals would supplement the typical aims of safety assessment, dose finding, and preliminary efficacy assessment.

To assess efficacy, the study should continue for 6 months and include biopsy examinations performed before and just after treatment. Patients with Ishak scores of 3-4, and possibly those with scores of 5-6, might be included, given that later studies would most likely include such patients. Conversely, if early trials include only patients with rapidly fibrosing phenotypes, the study period need not be greatly extended. These phenotypes include patients aged 40 years or older, men, and heavier patients, as well as any populations with genetic predeterminates. Because it might take considerable time for the actual measurable degree of fibrosis to change or regress definitively, smooth-muscle α-actin staining might serve as a primary efficacy end point.

The pivotal registrational study would examine treatment effects on fibrosis progression in patients with HCV or NASH and moderate fibrosis at baseline. Treatment likely would continue for 12-24 months, with prevention of cirrhosis as the regulatory end point. Computerized morphometry, immunohistochemistry, and gene expression studies could be secondary end points. The end point also could be categorized as a rank-order assessment of the total fibrosis score, the proportion of patients progressing by 1 stage, the proportion of patients remaining the same or improving by 1 stage, or time to events. The power calculations would vary depending on how the end point is defined and must account for sampling error, a placebo effect of up to 20%, and inadequate biopsy samples. The study design would include an extensive validation of both biomarkers and liver stiffness.

Table 3. Current Long-Term Studies in Liver Fibrosis

	HALT-C[34]	EPIC-3[35]	COPILOT[36]
Patient stage	Ishak 3–6	Metavir 2–4	Ishak 3–6
n	1000	2200 (3 studies)	600
End point	Fibrosis/clinical	Fibrosis/clinical	Clinical
Arm 1	Peg-IFN alfa-2a 90 μg	Peg-IFN alfa-2b 0.5 μg/kg	Peg-IFN alfa-2b 0.5 μg/kg
Arm 2	Observation	Observation	Colchicine
Run-in phase	Yes	Yes	No
Treatment duration, y	3.5	4	4
Recruitment status	Year 2 complete	Enrolling	Midpoint analysis

HALT-C, Hepatitis C Antiviral Long-term Treatment against Cirrhosis trial; EPIC-3, Evaluation of PegIntron in Control of hepatitis C cirrhosis study; COPILOT, COlchicine versus Peg-Intron LOng Term trial; IFN, interferon; Peg, pegylated.

Current Initiatives in Antifibrotic Treatment

A number of initiatives to evaluate antifibrotic treatment currently are ongoing. The largest clinical trial completed to date is the AEGIS (Anti-fibrotic Efficacy Gamma Interferon Study) of interferon γ vs placebo in patients with advanced HCV (Ishak 5 or 6), which failed to show a treatment benefit on fibrosis using liver biopsy examination as an end point.[34] The basis for this study was the observation that interferon γ inhibits stellate-cell activation and extracellular matrix production with a subsequent decrease in liver fibrosis in a model of liver injury.[35] A criticism of this study was the relatively short treatment duration of 1 year and the inclusion of only patients with advanced disease. Other initiatives in HCV include several that have attempted to suppress viral replication and intrahepatic inflammation. They include the Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) trial,[36] the international Evaluation of PegIntron in Control of hepatitis C (EPIC-3) cirrhosis study,[37] and the COlchicine versus Peg-Intron LOng Term (COPILOT) trial (Table 3). All of these studies use low-dose peg-interferon as the potential antifibrotic therapy. Primary end points include the clinical outcomes of death, transplantation, variceal/portal hypertensive bleeding, liver failure, and hepatocellular carcinoma. Evaluation of fibrosis is also an end point in these trials. In an interim analysis of the COlchicine versus Peg-Intron LOng Term trial, a difference in clinical end points has been seen between treatment arms at 2 years.[38] Interestingly, the benefits may be mediated by interferon's effect on reducing portal pressure and not necessarily on measurable fibrosis.[39] This illustrates the multiple variables that can affect clinical outcomes and the difficulty of linking liver fibrosis to eventual clinical outcomes.

The REGRESS study is a planned 5-year, 7-country study of 1000 patients with cirrhosis caused by HCV infection who have undergone antiviral therapy. Patients who have sustained viral eradication will be enrolled and compared with those who have not in terms of histologic and clinical end points.

Finally, the NASH Clinical Research Network is developing both a database and registry that will help define the natural history of NASH and fatty liver disease and a clinical trial of pioglitazone vs vitamin E vs placebo.[40] The study design is to enroll 240 patients at 8 centers and to assess biopsy specimen changes in NASH and liver fibrosis after 96 weeks of treatment.

Final Recommendations

Agreement on the clinical significance of preventing fibrosis progression and cirrhosis as a clinically acceptable surrogate for registration studies of antifibrotic agents is a significant first step forward. The ideal study population would comprise a homogenous group of HCV and NASH patients at high risk for fibrosis progression so that treatment differences could be detected more easily. Continued work toward the development of validated biomarkers also will reduce the size and complexity of antifibrotic trials.

We recommend the formation of a working group on surrogate end points for fibrosis comprising representatives from academics, industry, and regulatory authorities. This group ultimately could develop specific guidelines for using fibrosis as an end point in trials of liver disease.

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International Fibrosis Group Meeting Participants and their affiliations are listed in the Appendix (see supplementary material online at www.cghjournal.org).

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Appendix

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