CURRENT TREND

Treatment of liver fibrosis: Clinical aspects

Traitement de la fibrose hépatique : aspects cliniques

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Summary The main objective of antifibrotic treatment is to avoid the complications of chronic liver disease where its cause cannot be treated. Three main therapeutic endpoints can be targeted: cause; comorbidity; and fibrosis. Antifibrotic treatment is any intervention independent of cause that is intended to modify the course and/or level of fibrosis through direct action on the mechanisms of fibrosis. Several modalities are here considered: reduction of fibrosis course; reversion of fibrosis; and reversion of cirrhosis. Semiquantitative histological staging and morphometry are complementary techniques for monitoring fibrosis. The degree of fibrosis should preferentially be estimated by fibrosis progression based on measurements taken at baseline and during treatment, rather than by raw static measurements. Surrogate markers are the only tools for assessing drug efficacy in clinical practice, and are especially useful for checking compliance and identifying poor or non-responders. We propose to define non-response as no decrease in fibrosis progression. The renin–angiotensin system is a good candidate target for antifibrotic treatment, and angiotensin-II type-1 receptor blockers, such as sartans, are probably effective. Clinical trials are currently ongoing using marketed drugs, while new multitargeted drugs are likely to emerge from basic research.

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Résumé Le but principal du traitement antifibrosant est d’éviter les complications des hépatopathies chroniques où la cause ne peut pas être traitée. Trois principales options thérapeutiques peuvent être ciblées : la cause, les comorbidités et la fibrose. Le traitement antifibrosant doit être défini comme toute intervention indépendante de la cause et destinée à réduire l’évolution ou le niveau de fibrose grâce à une action directe sur les mécanismes de la fibrose. Plusieurs modalités doivent être considérées : une diminution de l’évolution de la fibrose, une réversion de la fibrose, une réversion de la cirrhose. Les classifications histologiques semi-quantitatives et la morphométrie sont des techniques complémentaires pour surveiller la fibrose. Le degré de fibrose devrait être préférentiellement estimé par la progression de la fibrose plutôt que par une mesure brute statique, à l’état basal et pendant le traitement. Les marqueurs de substitution seront le seul moyen de vérifier l’efficacité du traitement en pratique clinique, en particulier pour vérifier la compliance et pour détecter la non ou la mauvaise

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The treatment of liver fibrosis: Clinical aspects

Liver fibrosis is the histological expression of scarring as a result of chronic liver injury. Most pathological events lead to fibrosis after the initial parenchymal cell insult. This first event is responsible for primary lesions such as necroinflammation and/or liver steatosis. The development of liver fibrosis depends on several factors. The first is cause duration. Indeed, it is well accepted that fibrosis, at least at the significant level, usually occurs after a long period of time—usually months or even years. The second factor is comorbidity. Several arguments support the concept that the more comorbidity there is, the higher the level of fibrosis. The third factor is genetic determinants, as several genetic variants are known to interact with the mechanisms of fibrogenesis and fibrolysis [1]. All of these factors result in variable fibrosis progression [2].

There are several types of liver fibrosis at the histological level, and two main types of liver cells are involved in fibrogenesis. One type, found in the space of Disse around the sinusoids, is the hepatic stellate cell, mainly responsible for perisinusoidal fibrosis after myofibroblastic transformation. The second important fibrogenic cell is the portal myofibroblast, the cause of portal fibrosis. This means that there are two main types of liver fibrosis: perisinusoidal fibrosis; and portosetal fibrosis. The latter is quantitatively more abundant and is related to clinical complications such as portal hypertension. Perisinusoidal fibrosis can also lead to significant clinical consequences such as liver dysfunction and portal hypertension [3]. Nevertheless, other cell types, such as platelets, also play significant roles in fibrogenesis [4,5].

Whatever the cause, liver fibrosis appears to be a prerequisite for clinical complications [6]. Usually, these complications occur after the marked development of fibrosis such as cirrhosis, as seen in hepatocellular carcinoma in alcoholic chronic liver disease and hepatitis C. However, complications can arise before the cirrhotic stage, as seen in hepatocellular carcinoma in non alcoholic fatty liver disease (NAFLD) or in significant portal hypertension due to vitamin A intoxication [3].

The various therapeutic options for chronic liver disease include treating the causes and treating the consequences, which is, in turn, divided into the treatment of lesions such as liver fibrosis and the treatment of complications.

Prevention of hepatic fibrosis — and, thus, cirrhosis — may be the key to reducing healthcare costs and the overall burden of the disease. The lack of preventative measures, and of effective and affordable treatments, for these liver diseases highlight the importance of alternative therapeutic strategies such as novel antifibrotic agents [6].

Principles of treatment

The treatment of liver fibrosis relies on its pathogenesis (briefly described above), and has the following three main targets.

Causes

This is usually the main therapeutic option for liver fibrosis, and has several different approaches (Table 1). The intervention can be physical: the relief of biliary obstacles can reverse biliary cirrhosis. Blood withdrawal can also reverse marked fibrosis due to hemochromatosis. The intervention can be a behavioral therapy, as in NAFLD [7] or alcoholic chronic liver disease. A French study showed that the risk of cirrhosis was doubled in the north of France compared with the south, despite the same level of alcohol consumption, and the cirrhosis risk was also doubled with most alcoholic beverages compared with wine. However, in most instances, treatment is pharmacological. The list of causal treatments leading to fibrosis reversion is growing, and includes immunomodulators for autoimmune hepatitis and

Table 1. Chronic liver diseases in which liver fibrosis can be reversed by treating the causal factor (adapted from Rockey [44]).

<table>
<thead>
<tr>
<th>Disease</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B</td>
<td>Nucleoside/nucleotide</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>Interferon-alpha</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Bile-duct obstruction</td>
<td>Surgical decompression</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>Iron depletion</td>
</tr>
<tr>
<td>Alcoholic hepatitis</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td>Ursodeoxycholic acid</td>
</tr>
<tr>
<td>Non-alcoholic steatohapatitis</td>
<td>PPAR-gamma ligands</td>
</tr>
</tbody>
</table>

PPAR: peroxisome proliferator-activated receptor.
antiviral drugs for chronic hepatitis B and C infections (see other reports in this issue). Nevertheless, it should be borne in mind that several drugs, at least under certain circumstances, are profibrotic. Indeed, certain immunomodulators are deleterious in cases where chronic hepatitis C recurs after liver transplantation [8].

Comorbidity

Among the cofactors involved in fibrogenesis, comorbidity is especially important. The main culprits are components of the metabolic syndrome [9], which suggests that fibrosis treatment should take a multitargeted approach. The treatment of cirrhosis in non-responding patients with chronic hepatitis C, for example, should consider the following targets: the metabolic syndrome; arterial hypertension; and hepatitis C, for example, should consider the following targets: the metabolic syndrome; arterial hypertension; and

Fibrosis

When treating the cause is either not possible or fails, then the treatment of fibrosis should be considered. Antibiotic treatment can be any intervention (independent of cause) that is aimed at reducing the course and/or level of fibrosis through direct action on the mechanisms of fibrosis. Its effects may be to reduce fibrogenesis and/or to favor fibrosis.

Evaluating fibrosis progression and therapeutic targets

Clinical objectives

There is no single clinical objective for antifibrotic treatment from a clinical perspective, although several objectives may be considered [10].

Reduction of fibrosis course

Recent data suggest that the average trend in chronic hepatitis C leads to cirrhosis in the elderly. This suggests that any treatment that reduces fibrosis progression even moderately, and provided its administration is sufficiently early, is likely to have a significant impact on public health.

Reversion of fibrosis

The goal here is to reverse the progression of fibrosis (the progression becomes negative). This guarantees that a non-cirrhotic patient will not evolve into cirrhosis. A stopping effect with null progression will have the same effect.

Reversion of cirrhosis

This is a special case, as there is still an ongoing debate over its definition. Briefly, the main objective is to reduce and suppress the residual risk of complications. At present, there are several ongoing studies attempting to assess whether or not cirrhosis reversion will also reduce the risk of complications [11]. Indeed, recovery from cirrhosis can be limited by cross-linkages [12]. It is also possible to distinguish between antifibrotic tools that reduce (or slow) fibrosis progression and those that reverse it (fibrosis reversion) in the specific setting of cirrhosis. In future, our discussions need to be focused on whether or not these therapeutic goals are applicable to clinical trials and/or clinical practice. However, at present, clinical trials constitute the main context of the following lines of investigation.

Duration

As with the clinical objective, there is no definitive guideline for treatment duration. Most of the current randomized trials are designed to test the drug effect for 2 years. In fact, this mainly depends on sample-size calculation which, itself, usually relies on the main outcome. Therefore, we need to examine the various ways of measuring liver fibrosis.

The main classifications of liver fibrosis use semiquantiative staging systems such as METAVIR and the Ishak system. The former is popularly used, but the second is more precise. However, both are observer-dependent, and the variability increases as a function of stage number [13]. Another issue is how to use these stagings to evaluate drug effects. Usually, the ordered variable (staging) is transformed into a binary qualitative variable such as success/failure, and there is a definition such as ‘an improvement is regression by at least one stage, while other settings are failures’. To be clinically meaningful, a large number of patients need to be involved.

However, several authors are reluctant to use histological staging as quantitative variables. In practical terms, this involves comparing means or medians between treatment groups. The classical argument is that the scale of staging is non-linear. In fact, most data are drawn by plotting the stage against the amount of fibrosis, usually measured as the area of fibrosis. The corresponding scatter plot is the exponential increase in fibrosis amount versus stage that is mostly attributable to cirrhosis (Fig. 1a). However, the area of fibrosis is not a good reference point for evaluating stage linearity, as staging reflects architecture whereas the area of fibrosis reflects quantity.

A better technique to use is fractal geometry, a morphometric technique that measures the geometry of biological structures—in other words, their architecture. We have observed that the fractal dimension of liver fibrosis increases linearly as a function of fibrosis stage in chronic viral hepatitis using either METAVIR or Kleiner staging in NAFLD (Fig. 1b). For this reason, we believe that staging could be more simply used in therapeutic trials as a quantitative variable, but this will be even a matter of debate. However, for those who are reluctant to take this step, using the progression rate (or speed) would partly circumvent any difficulty, as staging is divided by duration, which provides a numerical unit such as METAVIR units per year (MU/year).

New measurements by morphometry

One way to circumvent the previous limitations of liver histology is to use morphometry. This term refers to the quantitative measurement of one or more histological characteristics. The best-known technique measures the fibrotic surface using different methods. The area of fibrosis is usually expressed as the percentage of fibrosis of the whole liver surface [14]. One advantage is that it is easier to handle in statistics and, consequently, allows the sample
size to be reduced—in other words, it is a more sensitive variable than staging. In fact, a significant drug effect has been demonstrated in several trials using morphometry, whereas no significant effect was found with staging [15,16].

However, there are drawbacks: as the technique is not standardized, values of the area of fibrosis are not comparable in the literature; and the clinical significance has yet to be determined.

For this reason, we propose applying the previously mentioned objective: reduction of progression or reversion. Indeed, staging and morphometry are complementary. In cirrhotic patients, cirrhosis presence or reversion is diagnosed according to the pathologist’s opinion whereas the fibrosis course is better evaluated by morphometry. The limitation of using the area of fibrosis is compensated for by the use of fractal dimensions, which reflect both the architecture and quantity of liver fibrosis (Fig. 2).

Two animal models have established that fractal dimensions of liver fibrosis are highly sensitive for the detection of pharmacologically induced changes [17]. In addition, fractal-dimension measurements are much less sensitive to biopsy specimen length, as is usually seen when assessing area of fibrosis.

Furthermore, morphometry was able to show a significant change in liver fibrosis in a small series of patients with different histological stagings [15] (Fig. 3, with personal data). In spite of this, staging is still being used as a reference point. However, morphometry, which is now fully automated, should not be considered a competitor, but a complementary tool that is able to detect subtle changes, requires fewer patients and a shorter time to detect an effect.

**Surrogate markers**

The recent interest in surrogate markers is linked to the limitations of liver biopsy (sampling and observer variability, cost, morbidity and discomfort). A growing number of studies now suggest that non-invasive markers (ultrasonographic elastometry such as Fibroscan, blood tests) can reflect drug effects in liver fibrosis [18,19]. It should be remembered that hyaluronic acid is a marker that is usually abnormal in perisinusoidal fibrosis [20]. However, the quality of surrogate markers needs to be validated by comparison with histological evaluations before it can be recommended as the sole marker. Indeed, it is known that there may be a dissociation between certain surrogate makers validated on baseline conditions and on liver lesions following pharmacological intervention.

Some studies have shown that the results of these markers paralleled those of fibrosis evaluated on liver specimens. Both methods are becoming increasingly popular, but this must not be an effect of “fashion” as, otherwise, there is a risk of considering a cosmetic effect as a true reflection of liver status. Nevertheless, the use of surrogate markers

**Figure 1** Relationship between the area and fractal dimension of liver fibrosis and fibrosis staging in 204 patients with non-alcoholic fatty liver disease (unpublished data from Calès et al. [45]).

**Figure 2** The fractal dimension of liver fibrosis (x-axis) reflects both the architecture, expressed as Kleiner fibrosis stage (F, right y-axis), and amount (area) of fibrosis (left y-axis), in 204 patients with non-alcoholic fatty liver disease (unpublished data from Calès et al. [45]).
needs to be systematically included in therapeutic trials so that, when it is demonstrated that a treatment has been effective, any correlation can be determined between the validated surrogate markers and liver lesions. This would allow evaluation of drug efficacy in clinical practice using surrogate markers as well as determining levels of compliance and identifying poor or non-responders. As for other chronic diseases, such as diabetes before the onset of complications or arterial hypertension, non-invasive markers could be a valuable tool for measuring drug effects.

In addition, as liver fibrosis is a lesion that progressively evolves over time, the measurement of fibrosis is easily repeatable with surrogate markers, and will probably reflect an effect of longer duration than will either glycemia, glycated hemoglobin or arterial pressure in metabolic syndrome.

It has also been suggested that portal pressure could be a surrogate marker of antifibrotic treatment [21].

**Drug trial design**

It is likely that a single drug treatment will have little value, as blocking one signalling pathway will be insufficient because of an escape or compensatory mechanism in another signalling pathway. However, it has been found that a drug can have several signalling impacts [22]. In any case, it appears to be difficult, from a methodological point of view, to begin controlled trials to test several drugs. Thus, the first step would be the classical comparison of an active intervention versus placebo, while the second step would be to test the drugs in combination [23].

**Candidate drugs**

A large number of targets are available in the treatment of liver fibrosis (Table 2), but one of the most promising is the signalling pathways. The renin-angiotensin system (RAS) is a putative candidate, the signalling pathway of which is described in Fig. 4. The RAS is currently viewed as part of a system of interconnected cytokines that become activated after tissue injury to promote tissue repair [24]. Hepatic fibrosis is associated with RAS activation [25]. The main inhibitors are targeted against angiotensin-converting enzyme (ACE). Angiotensin II also binds to angiotensin type 1 (AT1) or -2 receptors, which explains why blockade of the RAS with either ACE inhibitors or the newer AT1 receptor antagonists, or both, can significantly slow the progression of many fibrotic diseases. The novel angiotensin-(1-7) appears to play a protective role in hepatic fibrosis [25], and could be a new therapeutic target [26].

**Table 2** Targets of antifibrotic drugs in chronic liver diseases.

<table>
<thead>
<tr>
<th>Cytoprotective compounds</th>
<th>Reduced activation of liver stellate cells</th>
<th>Neutralization of cytokines</th>
<th>Inhibition of extracellular matrix synthesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostaglandins</td>
<td>Glucocorticoids</td>
<td>Pentoxifylline</td>
<td>Inhibitors of prolyl 4-hydroxylase</td>
</tr>
<tr>
<td>Silymarin</td>
<td>Interferons (α, β, γ)</td>
<td>Anti-TGF-β</td>
<td>Colchicine</td>
</tr>
<tr>
<td>Phosphatidylcholine</td>
<td>Retinoids</td>
<td>Bosentan</td>
<td>Halofuginone</td>
</tr>
<tr>
<td>Ursodesoxycholic acid</td>
<td>Estrogens</td>
<td>NO, NO donors</td>
<td></td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Prazosin</td>
<td>PPAR</td>
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<tr>
<td>S-adenosylmethionine</td>
<td>Sartans</td>
<td>Immunosuppressors</td>
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<td></td>
<td></td>
<td>(mycophenolate mofetil,</td>
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<tr>
<td></td>
<td></td>
<td>rapamycin)</td>
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<tr>
<td></td>
<td></td>
<td>Thiazolidinediones</td>
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</tr>
<tr>
<td>Zinc</td>
<td>ACE inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malotilate</td>
<td>Statins</td>
<td></td>
<td></td>
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<tr>
<td>Baicalein</td>
<td>Spironolactone</td>
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<tr>
<td>Rolipram (inhibitor of PDE4)</td>
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<td></td>
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<tr>
<td>Sildenafil</td>
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</tbody>
</table>

TGF: transforming growth factor; NO: nitric oxide; PPAR: peroxisome proliferator-activated receptor; ACE: angiotensin-converting enzyme.
The antifibrotic effect of inhibition of RAS activation has been observed in coronary heart disease, heart failure, diabetic nephropathy and stroke. Also, the beneficial effects on different measurements of liver fibrosis have been seen in more than a dozen studies of animal models of liver fibrosis [27], and at least three animal models of liver disease. Finally, at least six clinical studies have observed a putative beneficial clinical effect, and are briefly described here.

In patients with chronic hepatitis C, Terui et al. [15] tested the combination of losartan plus ursodesoxycholic acid versus ursodesoxycholic acid alone (controls). The 30 patients randomly included in the study had early-stage liver fibrosis. Levels of type IV collagen and plasma transforming growth factor (TGF)-β1 were significantly decreased in the losartan group compared with the controls, while histological staging showed no decrease in area of fibrosis compared with a significant decrease with losartan. In a non-randomized controlled study of 14 patients with chronic hepatitis C treated by losartan (50 mg/day for 6 months) compared with nine untreated controls, there was improvement in histological fibrosis, according to Ishak staging: −0.5 ± 1.3 in the losartan group versus +0.89 ± 1.27 in the control group (p < 0.03) [28].

Debernardi-Venon et al. [29] evaluated the effects of candesartan cilexetil (8 mg/day for 1 year versus no treatment) in 47 randomized cirrhotic patients. The level of hyaluronic acid was significantly decreased, as was portal pressure, but not levels of TGF-β1. No liver biopsy was performed. A retrospective study of 128 liver-transplant patients showed a significant decrease in fibrosis stage in the 27 patients treated with ACE inhibitors or sartans, as well as reductions in fibrosis progression and cirrhosis rate compared with the 101 untreated patients [30]. Also, the probability of cirrhosis was 35% versus 70% at 10 years, respectively (p = 0.0049).

A case-control non-randomized study of 284 patients with chronic hepatitis C, including patients treated with ACE inhibitors or sartans for arterial hypertension, was recently published [31]. Patients with hepatitis C and hypertension had increased fibrosis compared with non-hypertensive patients, but the hypertensive patients receiving angiotensin-blocking agents had less fibrosis than the hypertensive patients not using angiotensin-blocking agents. Yokohama et al. [32] observed a significant decrease in serum liver enzymes, blood markers of hepatic fibrosis and plasma TGF-1 levels in seven patients with non-alcoholic steatohepatitis and hypertension after losartan treatment. Furthermore, in contrast to cardiovascular outcomes in high-risk patients [33], angiotensin receptor blockers were superior to ACE inhibitors as liver antifibrosis agents in several studies.

However, only one of these clinical studies was a randomized trial including liver biopsy as the reference [15]. Moreover, the sample size was small, and the available infor-

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**Table 3** Drugs that have been tested for their effects on liver fibrosis.

<table>
<thead>
<tr>
<th>Very probable effects</th>
<th>Possible effects</th>
<th>Probably no effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors</td>
<td>Prostaglandins&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Ursodesoxycholic acid</td>
</tr>
<tr>
<td>Sartans</td>
<td>Silymarin</td>
<td>Vitamin E</td>
</tr>
<tr>
<td></td>
<td>Glucocorticoids</td>
<td>PDE-5 inhibitors</td>
</tr>
<tr>
<td></td>
<td>Retinoids&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Prazosin</td>
</tr>
<tr>
<td></td>
<td>Estrogens</td>
<td>Spironolactone</td>
</tr>
<tr>
<td></td>
<td>Endothelin antagonists</td>
<td>Pentoxifylline</td>
</tr>
<tr>
<td></td>
<td>(bosentan)</td>
<td>PPAR-α/-γ agonists</td>
</tr>
<tr>
<td></td>
<td>Immunosuppressors</td>
<td>Colchicine</td>
</tr>
<tr>
<td></td>
<td>CB2 agonists and CB1 antagonists (rimonabant)</td>
<td>Anti-TNF-α</td>
</tr>
<tr>
<td></td>
<td>Zinc</td>
<td>Imatinib</td>
</tr>
<tr>
<td></td>
<td>Somatostatin and analogs</td>
<td>Malotilate</td>
</tr>
<tr>
<td></td>
<td>Statins</td>
<td>Polynylphosphatidylcholine</td>
</tr>
<tr>
<td></td>
<td>Nitric oxide donors</td>
<td>Propylthiouracil</td>
</tr>
<tr>
<td></td>
<td>Amiloride</td>
<td>Pirfenidone</td>
</tr>
<tr>
<td></td>
<td>Interleukin-10</td>
<td>S-adenosylmethionine</td>
</tr>
<tr>
<td></td>
<td>S-adenosylmethionine</td>
<td>Interferon</td>
</tr>
</tbody>
</table>

<sup>a</sup> Possible profibrotic effects.

PDE-5: phosphodiesterase type-5; PPAR: peroxisome proliferator-activated receptor; TNF: tumor necrosis factor.
The primary aim of antifibrotic treatment is to avoid the complications in chronic liver disease in cases where the cause cannot be treated. The secondary goal is to facilitate fibrosis reversion when treating the cause is insufficient, as in cirrhosis. Further investigations in this setting need to look at whether or not antifibrotic treatment can modify the threshold of irreversibility of cirrhosis [41].

Factors influencing treatment choice

Three factors need to be taken into consideration: the degree of liver fibrosis; the cause of the chronic liver disease [42]; and the cofactors involved [43]. The degree of fibrosis should preferentially be estimated from fibrosis progression rather than from a raw static measurement. It appears to be more useful to treat a younger patient who is METAVIR stage F2 and has a rapid rate of fibrosis progression than an elderly patient with METAVIR stage 2, but who is more likely to have a slow rate of fibrosis progression. Thus, a rapid fibroser could become a slow fibroser with treatment without being considered a non-responder (Fig. 5).

As for cofactors, the risk factors for fibrosis progression and associated conditions should be considered. In such cases, a putative antifibrotic agent among the different drugs indicated for the condition, such as an angiotensin receptor blocker for arterial hypertension or diabetes, can be used.

Recommendations

In a patient with arterial hypertension in whom treatment is indicated, as defined above, changing to an angiotensin receptor blocker may be considered. However, if LDL cholesterol is increased, a statin should be prescribed. We suggest irbesartan (an angiotensin receptor blocker) because of its...

Figure 5  Progression of area of fibrosis in 157 patients with chronic hepatitis C (unpublished data from Calès et al. [46]). At least two sets of fibrosers can be distinguished according to progression rate. A fast fibroser may become a slow fibroser with antifibrotic treatment without being considered a non-responder.
low liver metabolism, beginning with a dose of 75 mg/day and reaching 150 mg/day in cases of good tolerability. A single dose administration in the evening is suggested. However, the drug should not be prescribed for patients with decompensated cirrhosis. Hepatotoxicity is extremely rare.

Conclusion

The main objective of antifibrotic treatment is to avoid the complications in chronic liver disease in patients in whom the cause cannot be treated. Nowadays, we have the means to determine the indications for, and to monitor, the antifibrotic treatment. We also have good putative candidates already on the market with possible indications when other condition(s) are associated with liver fibrosis. In other patients, concerted efforts should be made to manage any cofactors before the ongoing trials are completed in the hopes that the results will be positive. In addition, it is likely that new antifibrotic drugs will emerge from the basic research.

Author disclosure: Paul Calès, Frédéric Oberti have stock ownership in BioLiveScale Inc. that has a license for FibroMeter from Angers University.

References


