Title:

Early Decrease of Liver Stiffness after Initiation of Antiviral Therapy in Patients with Chronic Hepatitis C

Running title:

Early decrease of liver stiffness during antiviral therapy

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Keywords:

Chronic hepatitis C

Transient elastography

Fibroscan

Direct acting antiviral agents (DAA)

Word count: 628

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To the Editor: Liver elastography is widely used to assess liver fibrosis in patients with chronic hepatitis C and has also been recommended to monitor regression of liver fibrosis after successful antiviral therapy [1-3]. We studied early changes of liver stiffness after initiation of antiviral treatment.

The study population comprised 53 patients with chronic hepatitis C (mean age ± SD: 49.4 ± 10.7 years; METAVIR fibrosis stage F2, n=23; F3, n = 12; F4, n = 18; genotype (GT) 1, n = 32; GT3, n = 17; GT4, n = 4; mean BMI ± SD: 25.1 ± 3.8). All patients were treated with interferon-free all oral regimens. For each patient the individual treatment regimen was selected according to GT, fibrosis stage, pretreatment and current reimbursement policy of insurances. Prior to therapy and 1-6 weeks after initiation of antiviral treatment fibrosis stage was assessed by transient elastography using the Fibroscan® 502 Touch device with the M-probe (Echosens, Paris, France) and classified according to the METAVIR scoring system (F0 = no fibrosis; F1 = portal fibrosis without septa; F2 = portal fibrosis and few septa; F3 = numerous septa without cirrhosis; F4 = cirrhosis). Cut-off values for liver stiffness were defined as 7.1 kPa for F ≥ 2, 9.5 kPa for F ≥ 3 and 12.5 kPa for F = 4 [4]. Only procedures with 10 successful measurements of liver stiffness with an interquartile range < 30% were considered reliable.

Mean liver stiffness at baseline was 14.69 ± 11.15 kPa and decreased to 12.41 ± 9.83 kPa at follow-up Fibroscan® performed between week 1 and week 6 (p=0.006). (If more than one follow-up Fibroscan® between week 1 and week 6 was available in a patient, the mean was taken for this analysis). When the same Fibroscan® cut-off values applied at baseline were applied after initiation of antiviral therapy the following results were obtained: Within 6 weeks after initiation of treatment fibrosis stage improved by at least one stage in 23/53 (43%) patients, remained stable in 28/53 (53%) and worsened in 2/53 (4%). From the 23 patients classified as F2 at baseline, 11 (48%) were classified as F0/F1 at week 1-6, 10 (43%) as F2,

and 2 (9%) as F3. From the 12 patients classified as F3 at baseline, 3 (25%) were classified as F0/F1 at week 1-6, 4 (33%) as F2, and 5 (42%) as F3. From the 18 patients with F4 at baseline, 1 (6%) was classified as F0/F1 at week 1-6, 2 (11%) as F2, 2 (11%) as F3 and 13 (72%) as F4 (see Figure 1). Decrease of liver stiffness did not correlate with baseline AST (r=0.28) or ALT (r=0.04) levels.

In 18 of the 53 patients (F2, n = 8; F3, n = 4; F4, n = 6; mean BMI ± SD: 23.7 ± 4.0) Fibroscan® measurements were available at baseline, at week 1-2 and at week 4-6. In these patients mean liver stiffness was 13.05 ± 3.00 kPa at baseline, 10.01 ± 2.10 kPa at week 1-2 and 9.78 ± 4.89 kPa at week 4-6.

In our study a marked decrease of liver stiffness was observed within two weeks after initiation of antiviral therapy. From a pathophysiologic point of view a clinically significant decrease of liver fibrosis within such a short period of time seems impossible. We therefore assume, that the decrease is caused by resolution of the inflammatory activity within the liver. Inflammation has been shown to increase liver stiffness in chronic hepatitis C [5]. Current cut-off values for assessment of fibrosis stage in patients with chronic hepatitis C by transient elastography were obtained in patients with fibrosis *and* active inflammation. Therefore, our data clearly indicate that lower cut-off values for liver stiffness are appropriate for monitoring liver fibrosis after initiation of antiviral therapy.

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Figure legends:

Figure 1: Fibrosis stage at baseline and 1-6 weeks after initiation of interferon-free all-oral treatment of chronic hepatitis C in 53 patients.

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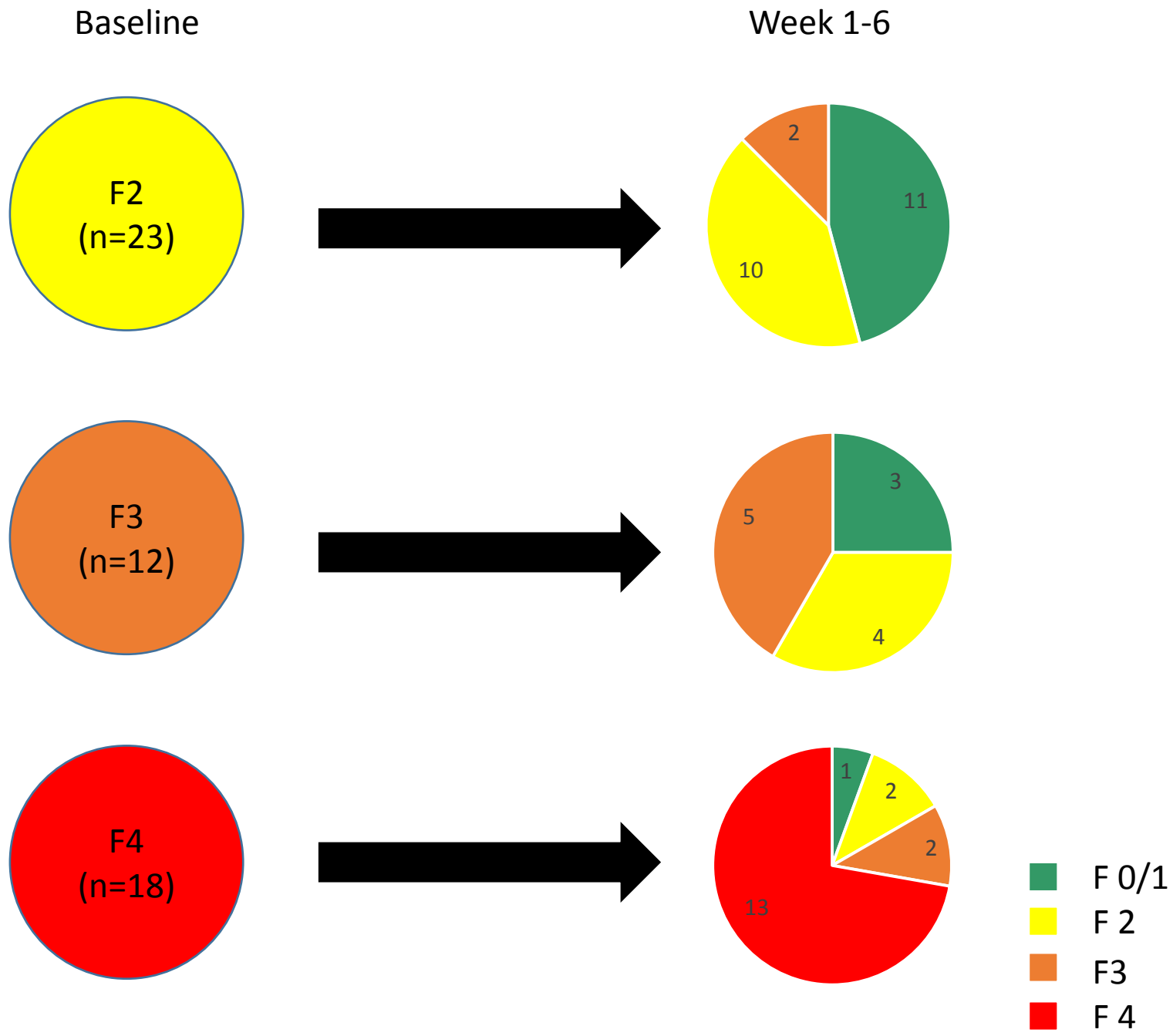
Michael Gschwantler: study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, study supervision, approval of the final draft submitted.

Financial support:

There was no financial support for this paper

Conflicts of interest:

Michael Gschwantler has participated in advisory boards for Janssen, MSD, BMS, AbbVie and Gilead. He has also served as speaker for Janssen, MSD, BMS, AbbVie and Gilead. All other authors have no conflicts of interest.


Baseline
Week 1-6
F2
(n=23)
2
11
10
F3
(n=12)
3
5
4
F4
(n=18)
1
2
2
13
F 0/1
F 2
F3
F 4