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Effects of telmisartan on liver fibrosis in patients with chronic liver disease

Effets du telmisartan sur la fibrose hépatique
au cours des hépatopathies chroniques

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Abbreviations

ACEI	Angiotensin converting enzyme inhibitor
AHT	Arterial hypertension
ALD	Alcoholic liver disease
ARB	Angiotensin II receptor blocker
CAP	Coefficient attenuation parameter
CLD	Chronic liver desease
DAP	Diastolic arterial pressure
NAFLD	Non-alcoholic fatty liver disease
PI	Prothrombin index
PPARγ	Peroxisome proliferator-activated receptor-γ
RCT	Randomized controlled trials
SAP	Systolic arterial pressure
VCTE	Vibration controlled transient elastography

PLAN

Effects of telmisartan on liver fibrosis in patients with chronic liver disease

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ABSTRACT

The role of angiotensin II receptor blocker (ARB) in the treatment of liver fibrosis is controversial. Telmisartan, an ARB PPARγ-agonist, could be an attractive alternative. Therefore, we performed a retrospective case control study evaluating the telmisartan effect on liver fibrosis. Methods: 77 patients with chronic liver disease were eligible and 66 included: 37 controls without ARB and 29 cases receiving telmisartan only during the study. Prior conventional ARB administration was permitted only in the telmisartan group. The primary judgement criterion (response) was defined as a relative decrease in vibration controlled transient elastography (VCTE) ≤ -10%. Results: patient characteristics were, median age: 57 years, male: 77%, NAFLD: 88% and median follow-up: 436 days. There were no significant differences between groups at baseline except for the followings, in telmisartan patients: more arterial hypertension treatment, ARB and oral antidiabetics, severe fibrosis and less alcohol intake or use. Response rate was, controls: 46% vs telmisartan: 55% (p=0.457). The independent predictors of response were, at baseline: alcohol intake, previous ARB, severe fibrosis, telmisartan group; and during follow-up: follow-up duration, anti-diabetics and variations in AST and waist circumference. However, there was a significant interaction between baseline ARB and telmisartan. Thus, the response rate depended on ARB status: controls: 46%, ARB-naïve telmisartan: 27%, ARB-experienced telmisartan: 72% (p=0.027 vs ARB-naïve telmisartan). This raw significant difference in response rate as a function of ARB status (p=0.048) was not maintained after adjustment on confusing factors in the whole population (p=0.435) but was maintained in the telmisartan group (p=0.017). Conclusion: in patients with liver fibrosis and treated by conventional ARB, a switch to telmisartan should be proposed.

INTRODUCTION

Liver fibrosis progression is a major factor in prognostication of chronic liver disease (CLD). The main treatment of liver fibrosis is the causal treatment. However, certain CLD causes have not yet specific treatment, especially non-alcoholic fatty liver disease (NAFLD) and alcoholic liver disease (ALD).

Angiotensin II is one of the main profibrotic factors [1]. Therefore, a lot of studies have evaluated the effects of angiotensin II receptor blockers (ARB) against fibrosis from cardiac, renal of liver origin. Thus, ARBs are indicated in the protection from diabetic nephropathy [2]. Concerning liver fibrosis, several controlled studies performed in animal models, one of them from our group [3], have shown an improvement by ARB. However, these results cannot be satisfactorily translated to human CLD since the ARB was often administered as a preventive drug in animal models. The next step was to observe the effects in humans, first with observational studies. Thus, several uncontrolled observational or retrospective case-control studies have suggested [4] or not [5] a beneficial effect against liver fibrosis. Four randomized controlled trials (RCT) are now available using liver fibrosis measured on liver biopsy as main outcome. The first used candesartan in ALD with positive results [6]. The second, from our group, tested irbesartan in a large cohort of chronic hepatitis C but the results were negative [7]. The third used telmisartan in NAFLD with positive result [8]. Finally, a recent study using losartan in NAFLD was inconclusive due to recuitment difficulties [9].

Telmisartan is an ARB, commonly used to treat arterial hypertension (AHT). Authors have reported a partial agonist effect on peroxisome proliferator-activated gamma (PPARg) receptor in addition to the blockade of the angiotensin II type 1 receptor [10]. This specificity

might explain interesting effects of telmisartan on liver fibrosis [11]. The main limiting factor in RCTs, whose main outcome is liver fibrosis, is liver biopsy requirement. However, non-invasive tests of liver fibrosis have gained large acceptance in recent years and some studies have shown they can be used as surrogate makers in antifibrotic therapy [12, 13]. As, on one hand, we use blood tests since 1997 [14] and VCTE since 2004 [15] and, on the other hand, we used telmisartan as reference ARB in CLD since our negative RCT [7] in our center, we have conducted a retrospective case control study to evaluate the effects of telmisartan by non-invasive tests of liver fibrosis. The main aim was thus to evaluate the changes measured by VCTE as this this the most validated non-invasive method [16].

PATIENTS AND METHODS

1. Patients

1.1. Characteristics

Patients were included into two groups: control and telmisartan. Inclusion criteria were CLD and age between 18 and 75 years. CLD etiology was NAFLD or chronic hepatitis C or alcohol or mixed previous causes. ARB administration prior to inclusion was permitted in the telmisartan group but not in the control group. Indeed, as telmisartan is not reimbursed for this indication in France, telmisartan administration often was a conversion of a previous ARB prescribed for another indication, mainly AHT. However, previous administration of telmisartan was not permitted in any group. Prior ARB was prescribed in 18 included patients: irbesartan: 7, candesartan: 4, valsartan: 3, losartan: 1 and olmesartan: 1. Patients should have non-invasive fibrosis test at inclusion and end of follow-up. Minimal follow-up duration was one year. Censoring date was the date of second non-invasive fibrosis test that was planned at the beginning of the second year. The date of inclusion was that of telmisartan in the telmisartan group and that of first available clinical work-up in control group. Non-inclusion criteria were change in ARB status during follow-up (no ARB in control group and telmisartan withdrawal in the telmisartan group), cirrhosis complication, specific causal treatment such as anti-HCV drug during the study or patients with previous HVC cure, liver transplantation and pregnancy. Patients were included between July 2004 (Fibroscan was available in April 2004 in our center) and January 2016 in the control group and between March 2009 and September 2015 in the telmisartan group.

The study was part of the SNIFF cohort including all CLD managed in our center started in September 1998 and regularly approved by French national health authorities in compliance

with successive laws or official rules. Written, informed consent was thus obtained from all patients.

1.2. Flow chart of patients

In this case control study, it was planned to have two paired (age and sex) controls for one case. However, it was not possible to obtain two paired controls for every case. So, the number of eligible patients was 77: 38 controls without ARB and 39 cases receiving telmisartan during the study. Three patients of telmisartan group were excluded since the time interval between inclusion date and date of baseline blood sample or VCTE was superior to 6 months. Additional 8 patients without VCTE available at inclusion or follow-up were excluded. This leaves a core population of 66 patients including 37 controls and 29 telmisartan patients (Figure 1).

2. Methods

2.1. Clinical and laboratory data

Demographic data, arterial pressure, liver function tests, serum creatinine, treatments, alcohol and tobacco consumptions were recorded at inclusion and end of follow-up. Alcohol use was considered as alcohol intake > 0 g/w.

Non-invasive fibrosis tests - Blood markers were those previously used in our blood tests to stage liver fibrosis in chronic viral hepatitis (FibroMeter^{V2G}) [17, 18] or NAFLD (FibroMeter^{NAFLD}) [19]. VCTE (Fibroscan, Echosens, Paris, France) was performed by experienced observers (>50 examinations before the study), blinded for patient data. Examination conditions were those recommended by the manufacturer [20]. VCTE examination was stopped when 10 valid measurements were recorded. Results (kPa) were expressed as the median of all valid measurements. Liver fibrosis staging was determined

according to VCTE classification [21]. Severe fibrosis (Metavir F3 and F4) was defined by median VCTE ≥ 10.9 kPa [21].

2.2. Telmisartan administration

The indication was based on the clinician opinion. Most cases were a switch from a conventional ARB to telmisartan. The indication of conventional ARB was usual indications such as AHT, heart failure and the protection from diabetic nephropathy. In other patients without prior conventional ARB, the telmisartan indication was either previous usual indications (condition diagnosed during the workup of CLD) or liver fibrosis following a previous positive candesartan RCT on liver fibrosis [6] and our negative RCT with Irbesartan [7]. The usual starting dose of telmisartan was 40 mg/d, then increased to 80 mg/d in the absence of side effects after a few days. The single administration was recommended at bedtime to avoid symptomatic arterial hypotension in early days.

2.3. Judgement criteria

The primary judgement criterion (also called simply response) was defined as a relative decrease in VCTE ≤ -10% i.e. ([measure at end of follow-up - measure at inclusion] / measure at inclusion) expressed in %. This was based on a clinically significant meaning. In addition, considering the median VCTE value, 10% change corresponds to a progression of around 1 kPa / year which has been shown to have prognostic value [22].

Secondary judgement criteria were relative changes in clinical descriptors of metabolic syndrome and tolerance (BMI, waist circumference, arterial pressure and creatinine), coefficient attenuation parameter (CAP) (Fibroscan, Echosens, Paris, France) and blood tests.

2.4. Statistics

Main comparisons were tested by non-parametric tests. Quantitative variables were expressed as median and 25% and 75% quartiles. Qualitative variables were expressed as

%. Comparison with adjustment used Mantel-Haenszel test for qualitative variables and ANCOVA for quantitative variables. Multivariate analysis of primary judgement criterion used backward stepwise binary logistic regression. Discriminant analysis was also used for subgroups analysis. Interaction between putative linked variables was also tested. Variables with collinearity (>0.8) were excluded except for those having significant interaction. The design of statistical analysis is detailed in Figure S1 in Supplemental material. The main statistical analyses were performed under the control of professional statisticians (SB, GH) using SPSS version 18.0 (IBM, Armonk, NY, USA).

RESULTS

1. Baseline characteristics

They are depicted in Table 1. Patients had a median age of 57 years and 77% were male. The main etiology was NAFLD (88%). This explains a mean BMI at 30.4 kg/m² and numerous previous treatments for AHT, diabetes and lipids. The mean VCTE was 10.3 kPa. The distribution of liver fibrosis classes was: F0/1: 0%, F1/2: 12.1%, F2: 45.5%, F3: 30.3%, F3/4: 1.5%, F4: 10.6%; thus, the prevalence of severe fibrosis was 42.4%. There were no significant differences between groups for most characteristics except for the followings. Telmisartan patients had a significant increase in severe fibrosis, waist circumference, treatment for AHT (due to ARB as expected) and oral antidiabetics. Conversely, they had less alcohol intake or use which was nevertheless moderate in the telmisartan group. The telmisartan dose (mg/d) was, median: 40 (25% and 75% quartiles: 40-80), mean: 52± 19.

2. Follow-up

The median follow-up was 436 days (370-568) and tended to be shorter in telmisartan group. At the end of follow-up, most of the same significant differences between groups were observed compared to baseline (Table 2). Thus, there was a significant increased prevalence of treatment for AHT and oral antidiabetics in telmisartan group. However, when comparing the changes in these characteristics between baseline and end of follow-up, we observed a significant decrease in alcohol intake and a significant increase in waist circumference in controls. By definition, there was a significant increase in ARB prescription in the telmisartan group. In this group, we also noticed a significant increase in vitamin E administration and a significant decrease in GGT and AST levels. This resulted in changes in significant differences between groups compared to baseline for the following characteristics: vitamin E

administration which became significantly increased in the telmisartan group whereas there was no more difference in alcohol intake between groups. Of note, as there was a trend to decreased angiotensin converting enzyme inhibitor (ACEI) prescription in the telmisartan group (in relationship with conversion to telmisartan), this resulted in a significantly higher ACEI administration during follow-up in controls. Importantly, the progression trends in severe fibrosis were opposite between groups so that the prevalence of severe fibrosis, which was significantly higher in the telmisartan group at baseline, became non significantly lower at end of follow-up.

3. Judgement criteria

3.1. Validation

The primary judgement criterion (VCTE change ≤ -10%) was retrospectively validated by a significant improvement in blood variables (liver enzymes) in responders compared to non-responders. The median variation in VCTE was -34% in response vs 19% in non-response ($p<0.001$) during follow-up.

3.2. Univariate analysis

The primary judgement criterion (VCTE change ≤ -10%) was observed in 50% of all patients without significant difference ($p=0.457$) between groups: 46% in controls vs 57% in telmisartan group (Table 3). Likewise, there was no significant difference between groups in any of the secondary judgement criteria (Table 3).

Predictors of the primary judgement criterion (VCTE change ≤ -10%) are reported for univariate analysis in Tables 4 to 6. Significant predictors were, at baseline: previous ARB, median VCTE, severe fibrosis; and during follow-up: variations in AST, ALT, GGT, VCTE and CAP.

3.3. Multivariate analysis

The independent predictors of the primary judgement criterion were evaluated by backward stepwise selection of variables including treatment group (forced entry), all significantly different variables at baseline or those during follow-up having a clinical impact on fibrosis (e.g. treatment). These variables included significant predictors of the primary judgement criterion as well as those significantly different between groups for adjustment. Independent predictors of VCTE change ≤ -10% were, at baseline: increased alcohol intake, previous ARB, severe fibrosis, treatment group; and during follow-up: longer follow-up duration and decrease in AST or waist circumference, anti-diabetics (absence) (Table 7). Surprisingly, telmisartan was a negative predictor of the primary judgement criterion. However, there was a significant interaction between previous ARB and telmisartan (p=0.074).

Therefore, we tested the relationship between the primary judgement criterion and treatment group as a function of previous ARB administration (Figure 2). The response rate differed between the three subgroups (p=0.048). In patients without previous ARB administration, primary criterion was reached in 45.9% of controls vs 27.3% of telmisartan group (p=0.313). In patients with previous ARB administration, any comparison was possible between treatment groups since ARB-experienced control patients were not included. In the telmisartan group, primary criterion was reached in 72.2% of patients with previous ARB administration vs 27.3% without (p=0.027). The difference between patients with telmisartan plus previous ARB and controls (without previous ARB) was not significant (p=0.066). This relationship between response and previous ARB administration was also observed whether primary judgement criterion (VCTE change ≤ -10%) was evaluated as a continuous variable (Figure 3) or VCTE variation evaluated either in relative change (delta VCTE) (Figure 4) or in progression between baseline and final VCTE values (Figure 5). Thus, this result was robust.

3.4. ARB subgroup comparison

Whole population - Due to the interaction between previous and ongoing ARB administration, we evaluated patient characteristics at baseline and end of follow-up (those of Tables 1 and 3) as a function of the three subgroups regarding ARB status: control (without ARB at baseline or during follow-up), telmisartan with previous ARB, telmisartan without previous ARB. The main significant differences were: at baseline alcohol intake ($p=0.018$) and severe fibrosis ($p=0.010$), and during follow-up VCTE change ≤ -10% ($p=0.048$) as expected (Table S1 in Supplemental material). By discriminant analysis, the only independent predictor of subgroups was severe fibrosis ($p<0.005$). Therefore, we tested the mean rate of the primary judgement criterion between these three subgroups adjusted on baseline severe fibrosis and/or alcohol intake (forced entry for sensitivity analysis) by ANCOVA (Table S2). The significant difference in primary judgement criterion between subgroups was not maintained after adjustment on the confusing factor(s).

Telmisartan group - Then, to further analyze the ARB impact in patients receiving telmisartan, characteristics of patients in the telmisartan group were compared as a function of previous ARB status at baseline (Table S3) and during follow-up (Tables S4 and S5). The only significant differences observed at baseline were, in patients with previous ARB, a smaller prevalence of ACEI (as expected), and a higher systolic arterial pressure. However, ACEI prevalence and systolic arterial pressure were not significantly different at end of follow-up. ARB patients had also more response (as expected). So, there was no confusing factor putatively explaining the difference in primary judgement criterion between telmisartan patients with or without previous ARB during the follow-up.

Finally, we evaluated response predictors in the telmisartan group (Table S6 to S8). In univariate analysis, predictors were, at baseline: previous ARB; and during follow-up: variations in ALT, AST and GGT. It should be noted that telmisartan dose did not significantly

influenced response rate (Table S3): mean dose was 50±19 in non-responders vs 53±20 mg/d in responders (p=0.709). In multivariate analysis, independent predictors were previous ARB (p=0.023) and AST variation (p=0.029) without significant role for severe fibrosis. Thus, the response rate was 29% in patients without previous ARB vs 71% (p=0.017) in patients with previous ARB after adjustment on AST variation by ANCOVA (Table S9). Main differences between ARB subgroups are summarized in Figures 6 and 7.

4. Side effects

Any significant impact of telmisartan was observed on serum creatinine and arterial pressures (Table 2).

DISCUSSION

Results

The main result is a lack of positive effect of telmisartan on the primary judgement criterion (VCTE change ≤ -10%) in univariate and multivariate analysis. However, in multivariate analysis, there was a significant interaction between baseline ARB and telmisartan. Therefore, we performed a subgroup analysis that showed that the response rate was significantly increased in patients treated by telmisartan with previous ARB compared to controls and even possibly compared to patients treated by telmisartan without previous ARB (borderline significance). In adjusted comparisons, the response was not maintained in the whole population but it was still significant in the telmisartan group.

The study design does not facilitate the interpretation since previous ARBs were permitted in the telmisartan group but not permitted in the control group. Indeed, 62% of telmisartan patients were previously treated by a different conventional ARB that was converted to telmisartan at the date of inclusion into the present retrospective study. It was not possible to have a control group with previous ARB administration since ARB withdrawal is a rare event. The easier intergroup comparison is that of patients without previous ARB since the only difference is the telmisartan introduction. There was a trend for a decreased response with telmisartan (Figure 2). However, this was due to the response definition since there was no significant difference (p=0.971) in relative VCTE change when this measurement was expressed in a continuous variable (Figure 4). Then, we should interpret the significant increase in response of telmisartan with previous ARB subgroup compared to patients with telmisartan without previous ARB or patients without telmisartan (controls). In these cases, this cannot be due to the response definition since there was a significant or a borderline

difference in VCTE change (measurement expressed in a continuous variable: Figure 4). So, it seems that the previous ARB administration conditions the telmisartan response. What are the explanations? First, it could be a type I error linked to post hoc subgroup analysis. However, this seems not very probable since these two characteristics are biologically strongly associated. Indeed, they share an action on the same receptor. Second, a confusing factor not recorded or not evaluated (like double interaction) cannot be ruled out. Third, a biological interaction has to be discussed. In that case, this would be the converse of tachyphylaxis which has not been described for ARB [23]. As the main difference between telmisartan and other ARBs is its partial agonist PPARγ effect [23], an interaction between receptors for angiotensin II type 1 and PPARγ might be suspected.

Finally, as this is a retrospective case-control study, a selection bias must be discussed. Comparison of telmisartan patients with controls showed some significant differences at baseline or at follow-up and these confounding variables were taken into account in the multivariate analysis. Although a selection bias not linked to recorded variables is possible, a selection bias linked to the main aim of the present study has to be discussed.

Indeed, there was an imbalance between groups regarding severe fibrosis and previous ARB. This means a significant increase in severe fibrosis in patients with previous ARB (Figure 6). This suggests a selection bias as patients with severe fibrosis with previous ARB could have been considered as non-responders to ARB and consequently switched to telmisartan. Conversely, it is probable that patients without severe fibrosis with previous ARB were considered as responders to ARB or not requiring telmisartan and thus maintained on the same ARB and not included in the present study. So, this clinical management prior to the study induced an enrichment in ARB non-response in patients with severe fibrosis. This is reinforced by a similar prevalence of severe fibrosis between controls and telmisartan ARB-

naïve patients (Figure 6). Finally, as response was higher in severe fibrosis (Figure 6), this explains, at least partially, the higher response rate observed in ARB-experienced patients. This relationship between response and fibrosis level has been observed with other drugs [25]. However, in the telmisartan group, a significant increased response persisted after adjustment on severe fibrosis in ARB-experienced patients (Figure 7). Taken together, whatever the eplanation(s), these data suggest that in ARB-experienced patients, preferably with severe fibrosis, a switch to telmisartan worth it.

Interpretation

The persistence of interaction between prior ARB and telmisartan after adjustment on fibrosis level suggests several explanations listed in Figure S2.

ARB RCTs

Four RCTs using histological outcome are available. The first evaluated the effect of candesartan (8 mg/d) versus AUDC during 6 months in subject with compensated ALD. This showed a significant improvement in liver fibrosis stage and area [6]. The second RCT evaluated the effect of irbesartan (150 mg/d) versus placebo during 24 months in chronic hepatitis C. No significant difference was found in liver fibrosis stage and area [7]. The third non-blinded RCT evaluated the effect of telmisartan (40 mg/d) versus lifestyle during 12 months in patients with NAFLD naïve of ARBs and ACEI. This RCT showed a significant improvement in composite histological outcome including activity and fibrosis [8]. The last RCT evaluated losartan (50 mg/d) versus placebo during 96 weeks in subject with NAFLD naïve of ARBs and ACEI. No histological improvement was observed but the study was underpowered due to recruitment deficit [9].

Limits

Several limits can be discussed. The small number of patients with fibrosis blood tests precluded their statistical use. There was no objective measurement of compliance since this information was qualitatively recorded in clinical files. Control patients with ARB were not available. The duration of previous ARB was not recorded. There was no direct evaluation of liver fibrosis but an indirect non-invasive evaluation by VCTE and blood tests. They have been shown to reflect antifibrotic therapy [12]. The duration of follow up was short for an anti-fibrotic evaluation; however, we have shown that certain non-invasive tests were more sensitive than liver morphometry to detect changes in fibrosis level over a two-year interval [26].

The results observed with previous ARB administration resulted from post hoc subgroup analysis that favors alpha risk; however, the biological plausibility of previous ARB counteracts this statistical limit.

Finally, the retrospective design is the most important imitation. This design and the small sample size make say that the present results should be considered as exploratory. Nevertheless, they encourage further study with prospective data recording and larger population.

Advantages

Previous therapeutic trials in NAFLD have shown null effects of verum tested. In several trials the verum evaluation was hampered by other intervention(s) (often drugs linked to metabolic syndrome such as ARB and ACEI) [9]. Thus, randomized trials on ARB in NAFLD are difficult to conduct. A case control study is an alternative study that allows to control

confusing factors encountered in clinical practice. Indeed, previous ARB administration was a non-inclusion criterion in RCTs testing ARB on liver fibrosis.

Application

The present study does not suggest a universal effect of telmisartan on liver fibrosis. However, the putative interaction with previous ARB administration and telmisartan suggest that previous ARB administration should be carefully taken into account in further trials either by considering only naïve patients (classical option but not supported by our results) or preferably by stratifying patients on previous ARB administration. In clinical practice, our results suggest that a patient with severe fibrosis with previous ARB could have a conversion to telmisartan in the absence or non-availability of other effective drugs.

Conclusion

The telmisartan response might be dependent on the previous ARB administration. A response was not observed in patients without previous ARB but a significant response was observed in patients already treated by ARB. This means that, in patients with CLD, severe fibrosis and conventional ARB, a switch to telmisartan should be proposed.

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TABLES

Table 1. Baseline characteristics of patients as a function of groups.

Variable	All patients			Control			Telmisartan		p [a]
	N	Value		N	Value		N	Value	
N total patients	66	-		37	-		29	-	-
Age (yr)	66	57.4 (49.9-63.9)		37	58.2 (48.6-64.3)		29	57.1 (51.1-63.8)	0.938
Sex (M)	66	77.3		37	78.4		29	75.9	0.809
NAFLD (%)	66	87.9		37	94.6		29	79.3	0.125
Metabolic sd (%)	66	82.6		37	80.0		29	90.9	0.658
Weight (kg)	66	89.5 (80.7-97.5)		37	88.0 (78.5-95.0)		29	90.0 (81.5-100.5)	0.393
Height (cm)	66	172 (162-176)		37	172 (161-176)		29	171 (164-175)	0.737
BMI (kg/m²)	66	30.4 (28.4-32.6)		37	30.0 (27.9-31.7)		29	30.4 (28.8-34.9)	0.256
Waist circumference (cm)	61	109 (102-118)		32	106 (99-118)		29	112 (108-119)	0.071
SAP (mm Hg)	60	130 (120-141)		37	130 (120-141)		23	132 (123-141)	0.517
DAP (mm Hg)	60	80 (71-85)		37	80 (71-84)		23	80 (71-86)	0.933
Alcohol (g/w)	62	0 (0-52)		35	30 (0-100)		27	0 (0-52)	0.005
Alcohol user (%)	62	43.5		35	57.1		27	25.9	0.014
Active tobacco (%)	66	16.9		37	18.8		29	14.8	0.741
Treatment (%):	66	-		37	-		29	-	-
AHT	66	63.6		37	45.9		29	86.2	0.001
ARB	66	27.3		37	0		29	62.1	<0.001
ACEI	66	19.7		37	24.3		29	13.8	0.286
Lipids	66	37.9		37	35.1		29	41.4	0.604
Insulin	66	7.6		37	5.4		29	10.3	0.647
Anti-diabetics PO	66	43.9		37	32.4		29	58.6	0.033
Vitamin E	66	1.5		37	2.7		29	0	1
AST (UI/l)	66	45 (34-60)		37	45 (34-58)		29	46 (31-62)	0.913
ALT (UI/l)	66	65 (46-87)		37	69 (45-891)		29	56 (48-81)	0.565
GGT (UI/l)	65	92 (41-177)		36	80 (40-212)		29	94 (43-158)	0.846
PI (%)	65	99 (92-106)		36	99 (91-106)		29	99 (91-105)	0.902
Creatinine (µmol/l)	58	74 (65-84)		35	75 (64-83)		23	74 (66-85)	0.892
VCTE (kPa)	66	10.3 (8.2-14.1)		37	10.1 (7.6-11.6)		29	11.5 (8.4-20.5)	0.057
Severe fibrosis (%)	66	42.4		37	29.7		29	58.6	0.018

SAP: systolic arterial pressure, DAP: diastolic arterial pressure, AHT: arterial hypertension, ARB: angiotensin receptor blocker, ACEI: angiotensin converting enzyme inhibitor, PI: prothrombin index VCTE: vibration controlled transient elastography.
Quantitative variables are expressed in median and 25-75% quartiles. N: patient number.
[a] Control vs telmisartan by Mann-Whitney U test or Pearson c² or Fisher exact test.

Table 2. Patient characteristics at end of follow-up: comparison either within each group between baseline (data from table 1) and end of follow-up, or between groups at end of follow-up (right column).

Variable	Control				Telmisartan			p [b]
	N	Follow-up	p [a]		N	Follow-up	p [a]	
Weight (kg)	35	88 (81-99)	0.067		29	92 (81-102)	0.176	0.571
Height (cm)	35	172 (165-176)	0.497		29	171 (164-174)	0.160	0.548
BMI (kg/m²)	35	30.3 (28.1-33.1)	0.062		29	31.2 (29.7-35.4)	0.165	0.212
Waist circumference (cm)	32	111 (100-115)	0.015		29	115 (105-122)	0.150	0.078
SAP (mm Hg)	26	138 (126-152)	0.096		29	135 (119-151)	0.877	0.567
DAP (mm Hg)	26	81 (73-86)	0.367		29	73 (65-84)	0.589	0.073
Alcohol (g/d)	34	0 (0-40)	0.008		29	0 (0-0)	0.673	0.141
Alcohol user (g%)	37	35.3	0.109		29	19.2	0.625	0.171
Active tobacco (%)	35	20.0	0.500		24	16.7	1.0	1
Treatment (%):	-	-	-		-	-	-	-
AHT	37	51.4	0.500		29	100	0.125	<0.001
ARB	37	0	1.0		29	100	0.001	<0.001
ACEI	37	27.0	1.0		29	6.9	0.500	0.035 [c]
Lipids	37	40.5	0.687		29	48.3	0.500	0.530
Insulin	37	8.1	1.0		29	10.3	1.0	1
Anti-diabetics PO	37	27.0	0.500		29	62.1	1.0	0.004
Vitamin E	37	13.5	0.219		29	41.4	<0.001	0.010 [c]
AST (UI/l)	37	38 (27-63)	0.626		29	36 (27-50)	0.049	0.336
ALT (UI/l)	37	59 (33-88)	0.502		29	56 (35-78)	0.250	0.851
GGT (UI/l)	36	70 (39-166)	0.061		29	80 (40-101)	0.005	0.579
Prothrombin index (%)	36	95 (89-104)	0.288		29	95 (88-102)	0.585	0.942
Creatinine (µmol/l)	35	78 (64-91)	0.124		29	75 (65-85)	0.531	0.639
VCTE (kPa)	37	9.1 (6.4-11.9)	0.521		29	9.4 (6.4-14.92)	0.023	0.514
Severe fibrosis (%)	37	35.1	0.804		29	41.4	0.125	0.604

Abbreviations: see Table 1. Quantitative variables are expressed in median and 25-75% quartiles. N: patient number.

[a] Paired comparison follow-up vs baseline by Wilcoxon test or McNemar c² de (the baseline sample size can be smaller than in Table 1).

[b] Control vs telmisartan at end of follow-up by Mann-Whitney U test or Pearson c².

[c] Changes in significant group differences between end of follow-up and baseline are indicated in red characters.

Table 3. Changes of quantitative variables during follow-up with comparison between groups.

Variable	All patients			Control			Telmisartan		p [a]
	N	Valeur		N	Valeur		N	Valeur	
N total patients	66	-		37	-		29	-	-
Follow-up (d)	66	436 (370-568)		37	456 (378-65)		29	383 (363-486)	0.072
Variations (%) [b]:	-	-	-	-	-	-	-	-	-
BMI	64	1.8 (-1.9-3.79)		35	1.8 (-1.0-3.6)		29	2.0 (-2.0-4.2)	0.984
WC	60	1.1 (-1.0-4.5)		31	2.0 (-0.8-5.7)		29	0.9 (-1.6-4.4)	0.332
SAP	42	3.7 (-6.3-12.7)		26	4.9 (-5.1-14.7)		16	1.4 (-10.5-10.9)	0.288
DAP	42	-0.6 (-10.4-12.9)		26	2.5 (-6.7-15.3)		16	-0.7 (-19.6-8.5)	0.277
AST	66	-8.5 (-30.7-14.9)		37	-3.8 (-27.1-16.4)		29	-12.1 (-36.8-13.9)	0.333
ALT	66	-10.9 (-33.2-20.9)		37	-11.1 (-27.0-21.2)		29	-9.9 (-38.3-24.7)	0.872
GGT	65	-14.0 (-40.2-10.7)		36	-12.1 (-37.7-14.6)		29	-15.0 (-46.2-3.0)	0.644
PI	65	-1.7 (-9.1-5.6)		36	-2.2 (-10.6-7.3)		29	0.0 (-8.6-5.2)	0.668
Creatinine	58	1.1 (-5.8-9.9)		35	3.8 (-5.6-14.0)		23	0.0 (-8.7-5.2)	0.146
VCTE	66	-10.3 (-34.3-18.8)		37	-5.9 (-29.2-23.6)		29	-15.0 (-44.5-10.6)	0.094
CAP	23	-9.0 (-23.2-1.6)		11	-1.2 (-18.9-10.3)		12	-11.6 (-26.2- -5.0)	0.268
FibroMeter V	17	-1.4 (-16.6-9.8)		6	2.8 (-11.3-36.0)		11	-4.6 (-17.0-9.1)	0.421
FibroMeter N	11	-1.1 (-17.4-12.5)		6	-9.3 (-52.3-14.1)		5	1.0 (-9.0-31.8)	0.273
FibroMeters	27	-1.3 (-17.0-10.4)		12	-1.2 (-24.3-21.7)		15	-4.6 (-16.1-10.4)	0.922
Alcohol (g/d)	58	0 (-22-0)		32	0 (-55-0)		26	0 (0-0)	0.019
VCTE ≤-10% (%)	66	50.0		37	45.9		29	55.2	0.457

Abbreviations: see Table 1; WC: waist circumference. Quantitative variables are expressed in median and 25-75% quartiles. N: patient

[a] Control vs telmisartan at end of follow-up by Mann-Whitney U test or Pearson c^2.

[b] Variations are relative changes except for alcohol (difference).

Table 4. Main baseline characteristics as a function of primary criterion (VCTE ≤-10%) reached.

Variable	No			Yes (response)		p [a]
	N	Value		N	Value	
N total patients	33	-		33	-	-
Age (yr)	33	58.2 (51.3-64.3)		33	56.7 (47.0-62.7)	0.363
Sex (M)	33	69.7		33	84.8	0.142
NAFLD (%)	33	84.8		17	90.9	0.708
Metabolic sd (%)	25	88.0		21	76.2	0.439
Weight (kg)	33	88.0 (78.5-95.0)		33	92.0 (81.5-100.5)	0.284
Height (cm)	33	171 (161-175)		33	172 (166-177)	0.140
BMI (kg/m²)	33	30.4 (28.5-34.1)		33	30.3 (28.4-31.6)	0.720
Waist circumference (cm)	31	109 (102-118)		30	109 (102-119)	0.818
SAP (mm Hg)	29	137 (125-143)		31	130 (120-138)	0.191
DAP (mm Hg)	29	80 (72-84)		31	79 (70-87)	0.965
Alcohol (g/d)	32	5 (0-77)		30	0 (0-22)	0.120
Alcohol user (%)	32	50.0		30	36.7	0.290
Active tobacco (%)	29	13.8		30	20.0	0.731
Treatment (%):	-	-		-	-	-
AHT	33	66.7		33	60.6	0.609
ARB	33	15.2		33	38.2	0.027
ACEI	33	27.3		33	12.1	0.122
Lipids	33	39.4		33	36.4	0.800
Insulin	33	12.1		33	3.0	0.355
Anti-diabetics PO	33	42.4		33	45.5	0.804
Vitamin E	33	0		33	3.0	1
AST (UI/l)	33	50 (33-61)		33	43 (32-61)	0.868
ALT (UI/l)	33	66 (44-88)		33	65 (50-86)	0.739
GGT (UI/l)	33	99 (39-180)		33	81 (43-180)	1
PI (%)	33	96 (90-106)		33	100 (93-105)	0.445
Creatinine (µmol/l)	32	73 (65-84)		30	75 (66-85)	0.827
VCTE (kPa)	33	10.2 (7.3-10.8)		33	11.8 (8.8-15.2)	0.037
Severe fibrosis (%)	33	24.2		33	60.6	0.003
Telmisartan group (%)	33	39.4		33	48.5	0.457

Abbreviations: see Table 1. Quantitative variables are expressed in median and 25-75% quartiles. N: patient number.
[a] Control vs telmisartan by Mann-Whitney U test or Pearson c².

Table 5. Main characteristics at end of follow-up as a function of primary criterion (VCTE ≤-10%) reached.

Variable	No			Yes (response)		p [a]
	N	Value		N	Value	
Alcohol (g/d)	29	0 (0-45)		31	0 (0-0)	0.306
Alcohol use (%)	29	34.5		31	22.6	0.307
Active tobacco (%)	28	17.9		31	19.4	0.883
Treatment (%):	-	-		-	-	-
AHT	33	78.8		33	66.7	0.269
ARB	33	39.4		33	48.5	0.457
ACEI	33	24.2		33	12.1	0.202
Lipids	33	36.4		33	51.5	0.215
Insulin	33	12.1		33	6.1	0.672
Anti-diabetics PO	33	42.4		33	42.4	1
Vitamin E	33	27.3		33	24.2	0.778
VCTE (kPa)	33	11.5 (7.6-15.0)		33	7.7 (5.5-9.7)	0.001
Severe fibrosis (%)	33	54.5		33	21.2	0.005

Abbreviations: see Table 1. Quantitative variables are expressed in median and 25-75% quartiles. N: patient number.
[a] Yes vs no by Mann-Whitney U test or Pearson c^2

Table 6. Variation in quantitative variables during follow-up as a function of primary criterion (VCTE ≤-10%) reached.

Variable	No			Yes (response)		p [a]
	N	Value		N	Value	
N total patients	33	-		33	-	-
Follow-up (d)	33	434(368-5608)		33	439 (374-569)	0.710
Variations (%) [b]:	-	-		-	-	-
BMI	32	2.3 (-0.8-4.2)		32	1.2 (-2.1-3.6)	0.324
Waist circumference	30	2.3 (0-5.8)		30	0.9 (-1.7-3.3)	0.080
SAP	20	6.6 (-0.8-16.3)		22	1.0 (-10.3-11.9)	0.174
DAP	20	-0.7 (-14.7-16.9)		22	0.1 (-8.6-10.1)	0.950
AST	33	8.0 (-12.0-17.7)		33	-18.6 (-39.9-5.8)	0.005
ALT	33	6.2 (-15.8-36.8)		33	-18.0 (-45.5-11.3)	0.005
GGT	30	-6.4 (-24.8-22.7)		28	-27.3 (-49.7- -4.3)	0.006
PI	33	-1.8 (-9.4-9.3)		32	-1.5 (-7.3-2.1)	0.577
Creatinine	33	-0.7 (-11.6-7.0)		33	2.5 (-4.6-14.9)	0.339
VCTE	33	18.5 (-0.7-33.6)		33	-33.7 (-49.5- -23.9)	<0.001
CAP	11	1.2 (-10.8-10.3)		12	-19.3 (-31.7- -8.8)	0.016
FibroMeter V	7	-1.1 (-6.2-6.9)		10	-10.3 (-22.8-11.8)	0.380
FibroMeter N	6	2.8 (-16.0-22.2)		5	-10.5 (-33.4-17.7)	0.273
FibroMeters	12	1.0 (-5.0-11.1)		15	-10.5 (-22.1-10.4)	0.172
Alcohol (g/d)	29	0 (-40-0)		29	0 (-15-0)	0.252

Abbreviations: see Table 1. Quantitative variables are expressed in median and 25-75% quartiles. N: patient

[a] Yes vs no by Mann-Whitney U test or Pearson c^2

[b] Variations are relative changes except for alcohol (difference)

Table 7. Independent predictors of primary criterion (delta VCTE ≤-10%). Backward stepwise binary logistic regression (54 patients).

Variable	Coeff. b	SD	Wald	p	Exp. (b)
At baseline:					
ARB (No=0, Yes=1)	3.349	1.779	3.545	0.060	28.478
Treatment group (C=0, T=1)	-3.913	1.860	4.428	0.035	0.020
Severe fibrosis at baseline (No=0, Yes=1)	4.881	1.810	7.270	0.007	131.730
Alcohol intake (g/w)	0.069	0.027	6.372	0.012	1.071
Follow-up:					
Anti-diabetics PO at follow-up (No=0, Yes=1)	-2.573	1.229	4.385	0.036	0.076
Follow-up duration (d)	0.013	0.006	4.748	0.029	1.013
Relative change in waist circumference	-48.543	21.142	5.272	0.022	0.000
Relative change in AST	-9.087	3.300	7.580	0.006	0.000
Constant	-5.464	3.010	3.294	0.070	0.004

List of variables (significant in univariate analysis for group an response) considered in the multivariate analysis: at baseline: VCTE, alcohol intake, waist circumference, group, ARB, severe fibrosis, AHT treatment, PO anti-diabetics; at follow-up: AHT treatment, ARB, delta waist circumference, follow-up duration, ACEI, vitamin E, PO anti-diabetics, difference in alcohol intake, delta AST, delta ALT, delta GGT. Variables with high colinearity and previous treatment without interaction were not included in the model. Note that follow-up variables deal with the entire follow-up period. Interaction of group with other treatments were: ARB baseline (p=0.074), anti-diabetics PO at follow-up (p=0.564).

FIGURES

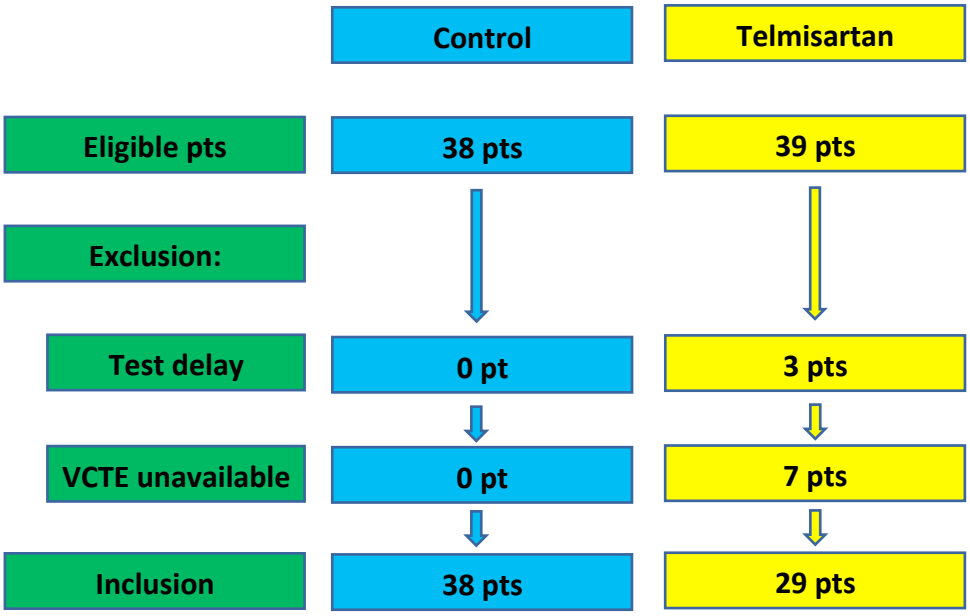

Figure 1. Flow chart of patients.

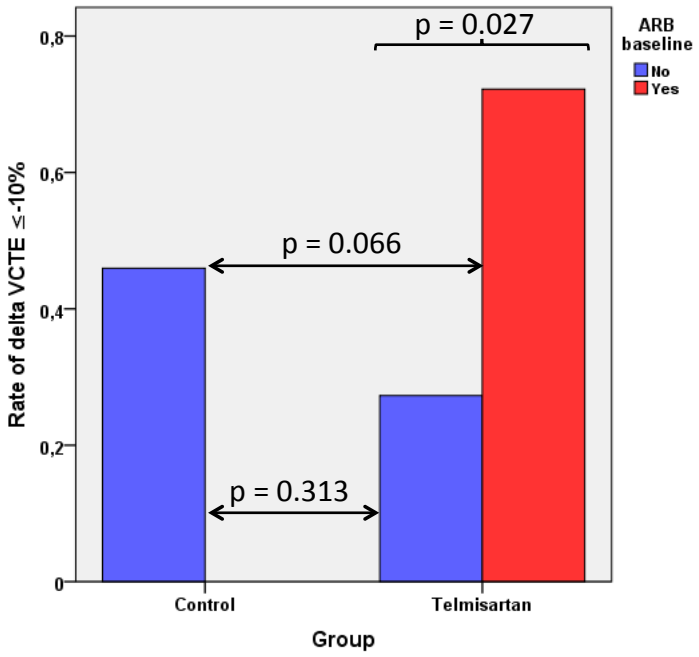

Figure 2. Rate of patients with primary judgement criterion (VCTE change ≤ -10% on Y axis) as a function of ARB status during follow-up (group on X axis) and at baseline (colored bar). The overall difference was p=0.048 by c^2 test. Pair differences were evaluated by c^2 test.

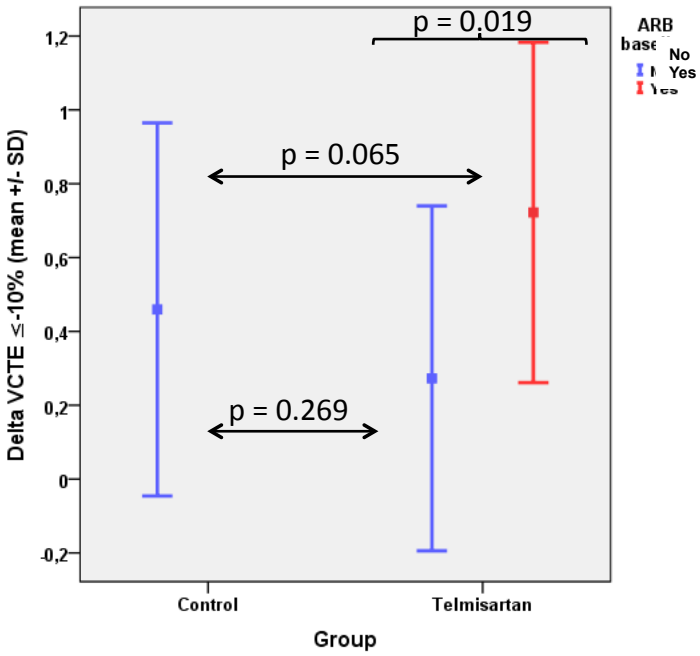

Figure 3. Mean rate ±SD of patients with primary judgement criterion (VCTE change ≤ -10% on Y axis) as a function of ARB status during follow-up (group on X axis) and at baseline (colored vertical lines). The overall difference was p=0.048 by ANOVA. Pair differences were evaluated by Student t test. This expression was used since box plots were not eloquent and parametric expression was used for adjusted means elsewhere.

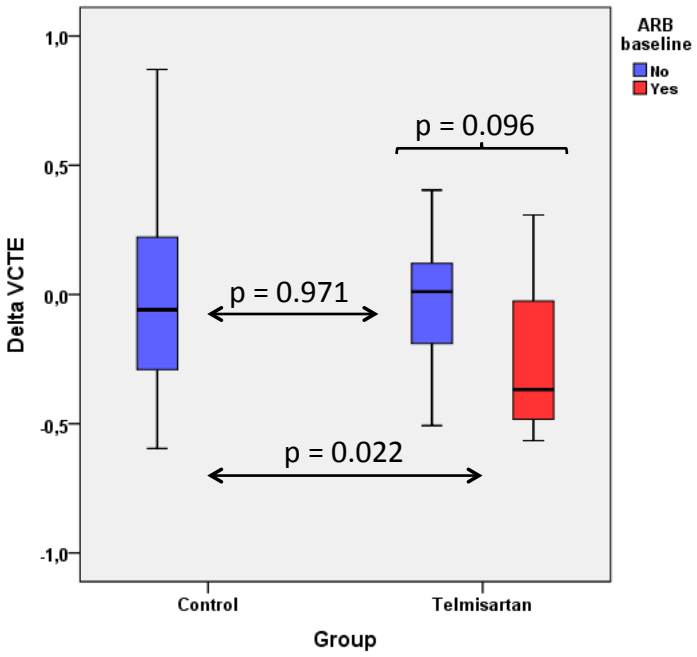

Figure 4. Relative changes in VCTE as a function of ARB status during follow-up (group on X axis) and at baseline (colored bar). Box plots depict median, 25 and 75% quartiles and extremes. The overall difference was p=0.050 by Kruskal-Wallis test. Pair differences were evaluated by Mann Whitney U test.

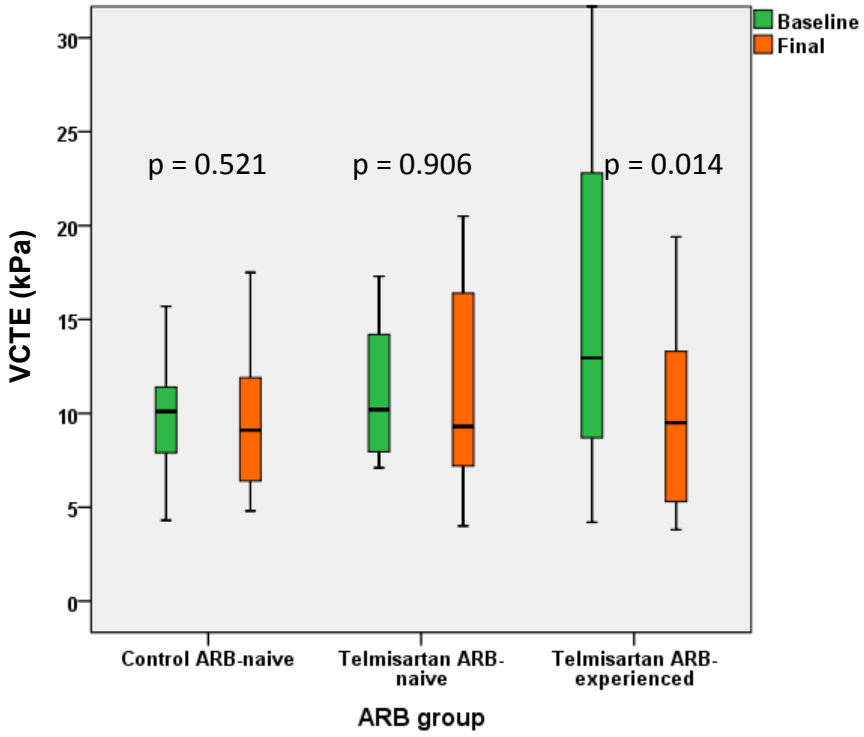

Figure 5. Comparison of VCTE values (Y axis) between baseline (orange bar) and end of follow-up (green bar) as a function of ARB status (X axis). Box plots depict median, 25 and 75% quartiles and extremes. Pair differences were evaluated by paired Wilcoxon test.

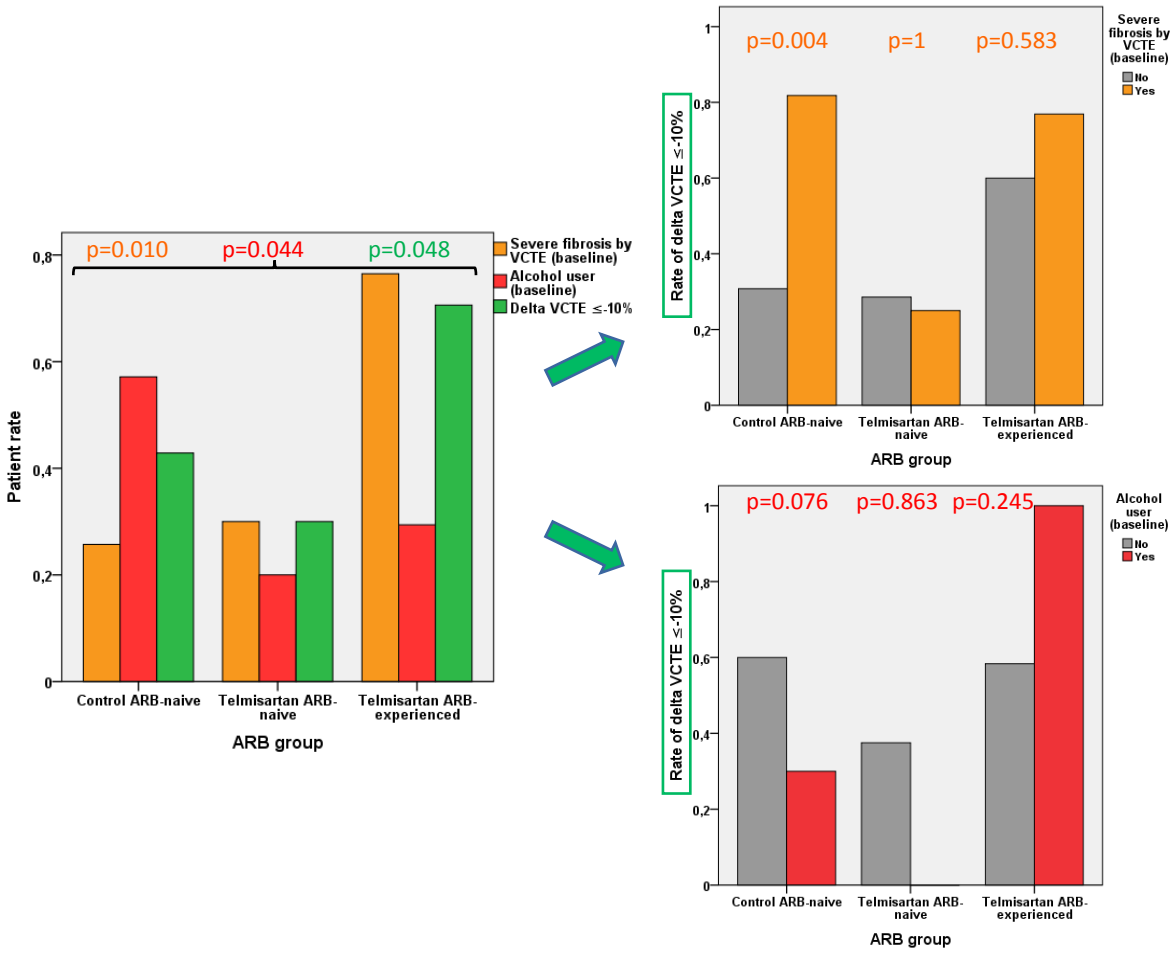

Figure 6. Rate of severe fibrosis, alcohol abuse and response in the whole population as a function of ARB status. The left panel shows that patients treated by telmisartan and ARB-experienced had more severe fibrosis and response (VCTE change ≤ -10%) and less alcohol abuse. The right top panel shows that ARB subgroups had different response rate after adjustment on severe fibrosis (p=0.029 by Mantel-Haenszel test), the impact of severe fibrosis being significant in controls. The right bottom panel shows that ARB subgroups had no significantly different response rates after adjustment on alcohol use (p=0.349 by Mantel-Haenszel test).

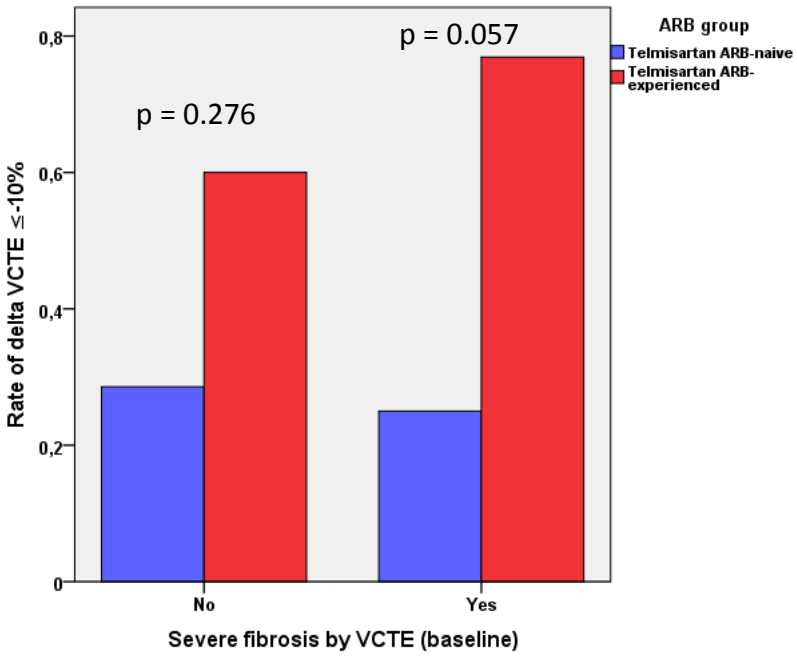

Figure 7. Rate of severe fibrosis and response in the telmisartan group as a function of ARB status.

ARB-experienced patients had more response than ARB-naïve patients (p=0.027 as raw data and p=0.047 after adjustment on severe fibrosis by Mantel-Haenszel test).

SUPPLEMENTAL MATERIAL

Table S1. Variables with significant (p<0.1) differences between ARB subgroups.

	Control (without previous ARB)	Telmisartan without previous ARB	Telmisartan with previous ARB	p [a]
N patients	37	11	18	-
Alcohol intake (g/d)	30 (0-100)	0 (0-15)	0 (0-20)	0.018
Alcohol user (%)	57.1	20.0	29.4	0.044
Severe fibrosis (%)	29.7	36.4	72.2	0.010
VCTE change ≤ -10% (%)	45.9	27.3	72.2	0.048
Follow-up duration (d)	456 (378-635)	455 (373-728)	377 (357-445)	0.045
Delta VCTE (%)	-5.9 (-29.2-23.6)	1.1 (-29.1-18.5)	-36.8 (-49.8-2.0)	0.059
Alcohol variation (g/d)	0 (-55 -0)	0 (0-0)	0 (0-0)	0.063

Quantitative variables are expressed in median and 25-75% quartiles. N: patient number.
[a] by Kruskal-Wallis test or Pearson c^2.

Table S2. Comparison of rate of primary criterion (delta VCTE ≤-10%) as a function of ARB subgroups and adjustment on variables with significant differences (in Table S1).

ARB subgroup	**Adjustment on:**			
	Without	**Alcohol**	**Severe fibrosis**	**Alcohol + severe fibrosis**
1. Control (%)	46±51	46±8	50±8	50±8
2. Telmisartan with previous ARB (%)	27±47	27±15	29±14	31±15
3. Telmisartan without previous ARB (%)	72±46	67±12	63±12	55±12
p[a]:	-	-		
All	0.048	0.124	0.200	0.435
1 vs 2	0.269	0.312	0.200	0.275
1 vs 3	0.065	0.163	0.386	0.732
2 vs 3	0.019	0.047	0.075	0.222

As quantitative alcohol intake was missing in 4 patients, alcohol was included as binary variable alcohol abuser.
[a] Without adjustment by ANOVA or with adjustment by ANCOVA followed by pair comparison.

Table S3. Main baseline characteristics in the telmisartan group as a function of previous ARB.

Variable	Without ARB			With ARB		p [a]
	N	Value		N	Value	
N total patients	11	-		18	-	-
Age (yr)	11	56.6 (53.3-57.3)		18	59.8 (48.2-66.7)	0.544
Sex (M)	11	63.6		18	83.3	0.375
NAFLD (%)	11	81.8		18	77.8	1
Metabolic sd (%)	5	100		6	83.3	1
Weight (kg)	11	90.0 (82.0-104.0)		18	92.0 (80.7-99.7)	0.636
Height (cm)	11	171 (161-175)		18	171 (166-176)	0.736
BMI (kg/m²)	11	30.4 (29.1-36.6)		18	30.4 (28.6-33.2)	0.653
Waist circumference (cm)	11	112 (108-123)		18	111 (106-119)	0.604
SAP (mm Hg)	8	123 (120-135)		15	138 (130-152)	0.052
DAP (mm Hg)	8	76 (67-84)		15	80 (74-87)	0.184
Alcohol (g/d)	10	0 (0-15)		17	0 (0-20)	0.845
Alcohol user (%)	10	20.0		17	29.4	0.678
Active tobacco (%)	10	10.0		17	17.6	1
Treatment (%):	11			18		
AHT	11	63.6		18	100	0.014
ARB	11	0		18	100	<0.001
ACEI	11	36.4		18	0	0.014
Lipids	11	36.4		18	44.4	0.717
Insulin	11	9.1		18	11.1	1
Anti-diabetics PO	11	63.6		18	55.6	0.717
Vitamin E	11	0		18	0	-
AST (UI/l)	11	46 (34-63)		18	46 (29-62)	0.719
ALT (UI/l)	11	61 (55-77)		18	54 (44-85)	0.529
GGT (UI/l)	11	116 (39-163)		18	80 (45-165)	0.702
PI (%)	11	104 (90-108)		18	98 (92-101)	0.500
Creatinine (µmol/l)	8	74 (68-87)		17	73 (64-83)	0.414
VCTE (kPa)	11	10.2 (7.3-17.3)		18	12.9 (8.6-23.8)	0.431
Severe fibrosis (%)	11	36.4		18	72.2	0.119

Abbreviations: see Table 1. Quantitative variables are expressed in median and 25-75% quartiles. N: patient number.
[a] Without vs with ARB by Mann-Whitney U test or Pearson c^2

Table S4. Main characteristics at end of follow-up in the telmisartan group as a function of previous ARB.

Variable	Without ARB			With ARB		p [a]
	N	Value		N	Value	
N total patients	11	-		18	-	-
Follow-up	11	455 (373-728)		18	377 (357-445)	0.105
Weight (kg)	11	92 (84-102)		18	92 (79-104)	0.529
Height (cm)	11	171 (162-175)		18	170 (166-174)	0.822
BMI (kg/m²)	11	32.0 (30.5-37.4)		18	30.8 (29.3-33.5)	0.323
Waist circumference (cm)	11	117 (108-123)		18	114 (104-121)	0.418
SAP (mm Hg)	7	129 (119-146)		10	136 (124-156)	0.494
DAP (mm Hg)	7	67 (53-84)		10	73 (70-86)	0.427
Alcohol (g/d)	10	0 (0-12)		16	0 (0-0)	0.969
Alcohol user (%)	10	20.0		16	18.8	1
Active tobacco (%)	9	11.1		15	20.0	1
Treatment (%):	17	-		19	-	-
AHT	11	100		18	100	-
ARB	11	100		18	100	-
ACEI	11	18.2		18	0	0.135
Lipids	11	36.4		18	55.6	0.316
Insulin	11	9.1		18	11.1	1
Anti-diabetics PO	11	72.7		18	55.6	0.449
Vitamin E	11	45.5		18	38.9	1
AST (UI/l)	11	42 (29-564)		18	35 (26-49)	0.431
ALT (UI/l)	11	66 (34-92)		18	49 (34-68)	0.281
GGT (UI/l)	11	88 (43-149)		18	58 (39-94)	0.271
Prothrombin index (%)	11	93 (85-104)		18	100 (89-102)	0.356
Creatinine (µmol/l)	7	85 (65-92)		16	72 (64-82)	0.216
VCTE (kPa)	11	9.3 (6.7-18.2)		18	9.5 (5.3-13.4)	0.589
Severe fibrosis (%)	11	45.5		18	38.9	1

Abbreviations: see Table 1. Quantitative variables are expressed in median and 25-75% quartiles. N: patient number.
[a] Without vs with ARB by Mann-Whitney U test or Pearson c²

Table S5. Changes of quantitative variables during follow-up in the telmisartan group as a function of previous ARB.

Variable	Without ARB			With ARB		p [a]
	N	Valeur		N	Valeur	
N total patients	11			18		-
Variations (%) [b]:						
BMI	11	2.4 (-1.9-4.9)		18	0.1 (-2.2-3.9)	0.393
Waist circumference	11	0.9 (-1.0-4.3)		18	0.4 (-2.2-5.5)	0.964
SAP	6	6.1 (2.4-11.3)		10	-4.9 (-13.9-11.1)	0.129
DAP	6	0.8 (-28.5-22.4)		10	-2.3 (-17.9-6.9)	0.914
AST	11	-12.1 (-50.3-9.5)		18	-10.2 (-36.1-16.3)	0.840
ALT	11	0 (-38.9-50.8)		18	-13.9 (-36.0-15.4)	0.559
GGT	11	-15.4 (-44.4-5.1)		18	-14.2 (-49.6- -0.8)	0.590
PI	11	-3.2 (-14.7-1.8)		18	1.0 (-3.9-5.3)	0.087
Creatinine	7	2.3 (-13.3-8.0)		16	-0.7 (-8.1-3.7)	0.548
VCTE	11	1.1 (-28.1-18.5)		18	-36.8 (-49.8-2.0)	0.096
CAP	11	-23.2 (-27.2-NA)		18	-10.8 (-23.6- -6.2)	0.782
FibroMeter V	4	-8.5 (-15.2- -1.9)		7	3.1 (-22.1-10.4)	0.705
FibroMeter N	1	ND		4	-3.2 (-9.8-38.6)	0.480
FibroMeters	5	-4.6 (-14.3-5.7)		10	-2.2(-18.3-11.8)	0.903
Alcohol (g/d)	10	0 (0-0)		16	0 (0-0)	0.803
VCTE ≤-10% (%)	11	27.3		18	72.2	0.027

Abbreviations: see Table 1. Quantitative variables are expressed in median and 25-75% quartiles. N: patient, NA: not available

[a] Control vs telmisartan at end of follow-up by Mann-Whitney U test or Pearson c^2 or Fischer exact test.

[b] Variations are relative changes except for alcohol (difference).

Table S6. Main baseline characteristics in the telmisartan group as a function of response (delta VCTE ≤-10%).

Variable	Without response			With response		p [a]
	N	Value		N	Value	
N total patients	13	-		16	-	-
Age (yr)	13	55.6 (48.9-62.3)		16	58.3 (53.0-65.2)	0.369
Sex (M)	13	69.2		16	81.3	0.667
NAFLD (%)	13	76.9		16	81.3	1
Metabolic syndrom (%)	5	80.0		6	100	0.455
Weight (kg)	13	88 (81-103)		16	92 (81-98)	0.878
Height (cm)	13	171 (163-173)		16	171 (163-179)	0.468
BMI (kg/m²)	13	30.84 (28.89-36.2)		16	30.5 (28.5-32.6)	0.776
Waist circumference (cm)	13	110 (106-120)		16	112 (108-119)	0.843
SAP (mm Hg)	13	137 (1224-140)		16	131 (123-153)	0.875
DAP (mm Hg)	13	80 (72-85)		16	79 (66-87)	0.776
Alcohol (g/d)	13	0 (0-0)		16	0 (0-20)	0.526
Alcohol user (%)	13	16.7		16	33.3	0.408
Active tobacco (%)	13	8.3		16	20.0	0.605
Treatment (%):	13	-		16	-	
AHT	13	76.9		16	93.8	0.299
ARB	13	38.5		16	81.3	0.027
ACEI	13	23.1		16	6.3	0.299
Lipids	13	38.5		16	43.8	0.774
Insulin	13	23.1		16	0	0.078
Anti-diabetics PO	13	61.5		16	56.3	0.774
Vitamin E	13	0		16	0	-
AST (UI/l)	13	46 (31-63)		16	45 (32-61)	1
ALT (UI/l)	13	61 (40-80)		16	55 (50-83)	1
GGT (UI/l)	13	105 (47-169)		16	85 (42-146)	0.677
PI (%)	13	100 (90-107)		16	97 (90-101)	0.661
Creatinine (µmol/l)	13	75 (71-86)		16	69 (57-83)	0.253
VCTE (kPa)	13	10.4 (7.3-14.6)		16	14.2 (8.6-25.9)	0.254
Severe fibrosis (%)	13	46.2		16	68.8	0.219

Abbreviations: see Table 1. Quantitative variables are expressed in median and 25-75% quartiles. N: patient number.
[a] Without vs with response by Mann-Whitney U test or Pearson c^2

Table S7. Main characteristics at end of follow-up in telmisartan group as a function of response (delta VCTE ≤-10%).

Variable	Without response			With response		p [a]
	N	Value		N	Value	
N total patients	13	-		16	-	-
Follow-up	13	391 (366-5493)		16	377 (359-488)	0.709
Weight (kg)	13	88 (83-104)		16	93 (79-102)	0.826
Height (cm)	13	170 (164-173)		16	171 (164-179)	0.496
BMI (kg/m²)	13	32.0 (29.0-36.4)		16	31.1 (29.7-32.7)	0.483
Waist circumference (cm)	13	112 (106-125)		16	115 (103-120)	0.553
SAP (mm Hg)	7	136 (119-156)		10	133 (124-144)	0.807
DAP (mm Hg)	7	63 (53-84)		10	73 (70-86)	0.281
Alcohol (g/d)	12	0 (0-0)		14	0 (0-5)	0.737
Alcohol user (%)	12	16.7		14	21.4	1
Active tobacco (%)	10	10.0		14	21.4	0.615
Treatment (%):	13	-		16	-	-
AHT	13	100		16	100	-
ARB	13	100		16	100	-
ACEI	13	7.7		16	6.3	1
Lipids	13	38.5		16	56.3	0.340
Insulin	13	23.1		16	0	0.078
Anti-diabetics PO	13	61.5		16	62.5	1
Vitamin E	13	53.8		16	31.3	0.219
AST (UI/l)	13	47 (31-65)		16	33 (24-41)	0.025
ALT (UI/l)	13	75 (41-98)		16	44 (34-65)	0.044
GGT (UI/l)	13	88 (42-156)		16	58 (36-92)	0.065
Prothrombin index (%)	13	93 (89-102)		16	100 (88-103)	0.455
Creatinine (µmol/l)	11	76 (65-88)		12	72 (64-82)	0.498
VCTE (kPa)	13	11.5 (7.6-16.4)		16	9.1 (5.3-13.3)	0.245
Severe fibrosis (%)	13	53.8		16	31.3	0.219
Telmisartan dose (mg/d)	8	40 (40-70)		12	40 (40-80)	0.273

Abbreviations: see Table 1. Quantitative variables are expressed in median and 25-75% quartiles. N: patient number.
[a] Without vs with response by Mann-Whitney U test or Pearson c²

Table S8. Variation in quantitative variables during follow-up as a function of primary criterion (VCTE ≤-10%) reached in telmisartan group.

Variable	No			Yes (response)		p [a]
	N	Value		N	Value	
N total patients	13	-		16	-	-
Variations (%) [b]:	13	-		16	-	-
BMI	13	2.7 (-1.0-4.8)		16	0.1 (-2.3-3.6)	0.254
Waist circumference	13	0.9 (0.0-4.8)		16	0.0 (-3.7-4.2)	0.254
SAP	6	7.9 (-1.2-11.3)		10	-4.6 (-13.9-8.7)	0.233
DAP	6	-13.4 (-28.5-16.9)		10	0.1 (-10.3-6.9)	0.447
AST	13	9.5 (-10.4-17.7)		16	-27.2 (-46.2- -7.0)	0.021
ALT	13	9.2 (-16.8-47.6)		16	-16.9 (-42.2-5.4)	0.028
GGT	13	-6.4 (-24.6-24.8)		16	-23.9 (-52.8- -13.1)	0.035
PI	13	-3.2 (-9.7-3.4)		16	0.1 ((-5.2-4.3)	0.292
Creatinine	11	-1.5 (-13.3-2.3)		12	0.6 (-7.7-7.3)	0.356
VCTE	13	15.6 (-0.7-26.9)		16	-42.7 (-53.3- -30.8)	<0.001
CAP	4	-7.3 (-23.1-2.4)		8	-16.1 (-26.4- -8.8)	0.396
FibroMeter V	3	-1.0 (-12.5-NA)		8	-10.3 (-20.8-10.1)	0.683
FibroMeter N	3	12.5 (0.1-NA)		2	-9.0 (-10.5-NA)	0.083
FibroMeters	5	3.1 (-6.8-31.8)		10	-9.3 (-18.3-9.4)	0.142
Alcohol (g/d)	12	0 (0-0)		14	0 (-5-0)	0.917

Abbreviations: see Table 1. Quantitative variables are expressed in median and 25-75% quartiles. N: patient, NA: not available

[a] Yes vs no response by Mann-Whitney U test or Pearson c^2

[b] Variations are relative changes except for alcohol (difference)

Table S9. Comparison of rate of primary criterion (delta VCTE ≤-10%) as a function of ARB subgroups and adjustment on baseline severe fibrosis (main confusing factor) or alcohol abuse or both in the telmisartan group.

ARB subgroup	**Adjustment on delta AST**	
	Without	**With**
Telmisartan with previous ARB (%)	27±47	29±13
Telmisartan without previous ARB (%)	72±46	71±10
p[a]	0.017	0.017

[a] Without adjustment by t test or with adjustment by ANCOVA

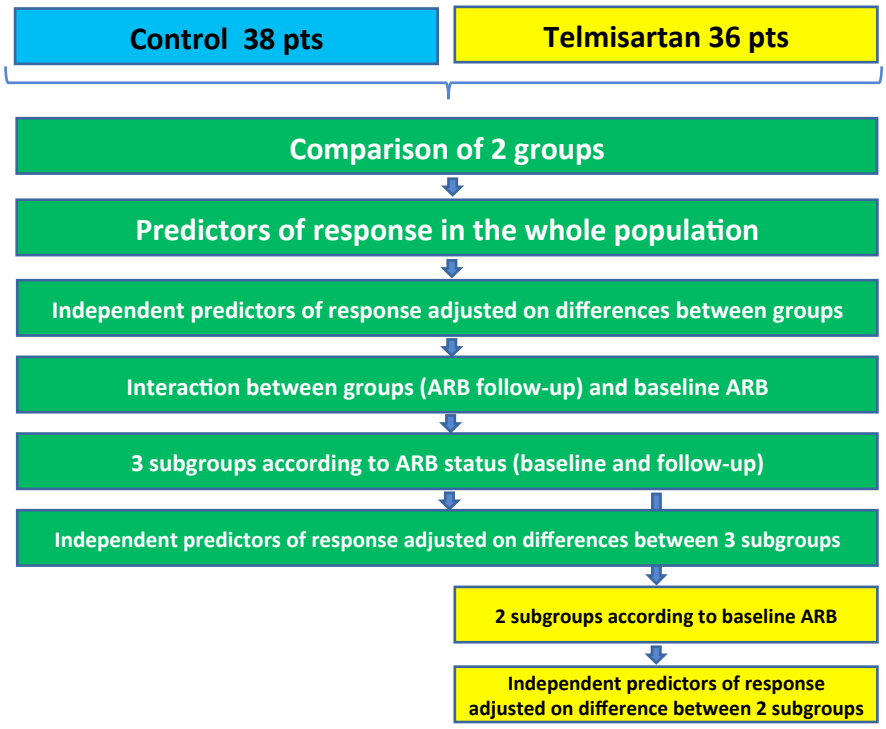

Figure S1. Design of the statistical analysis.

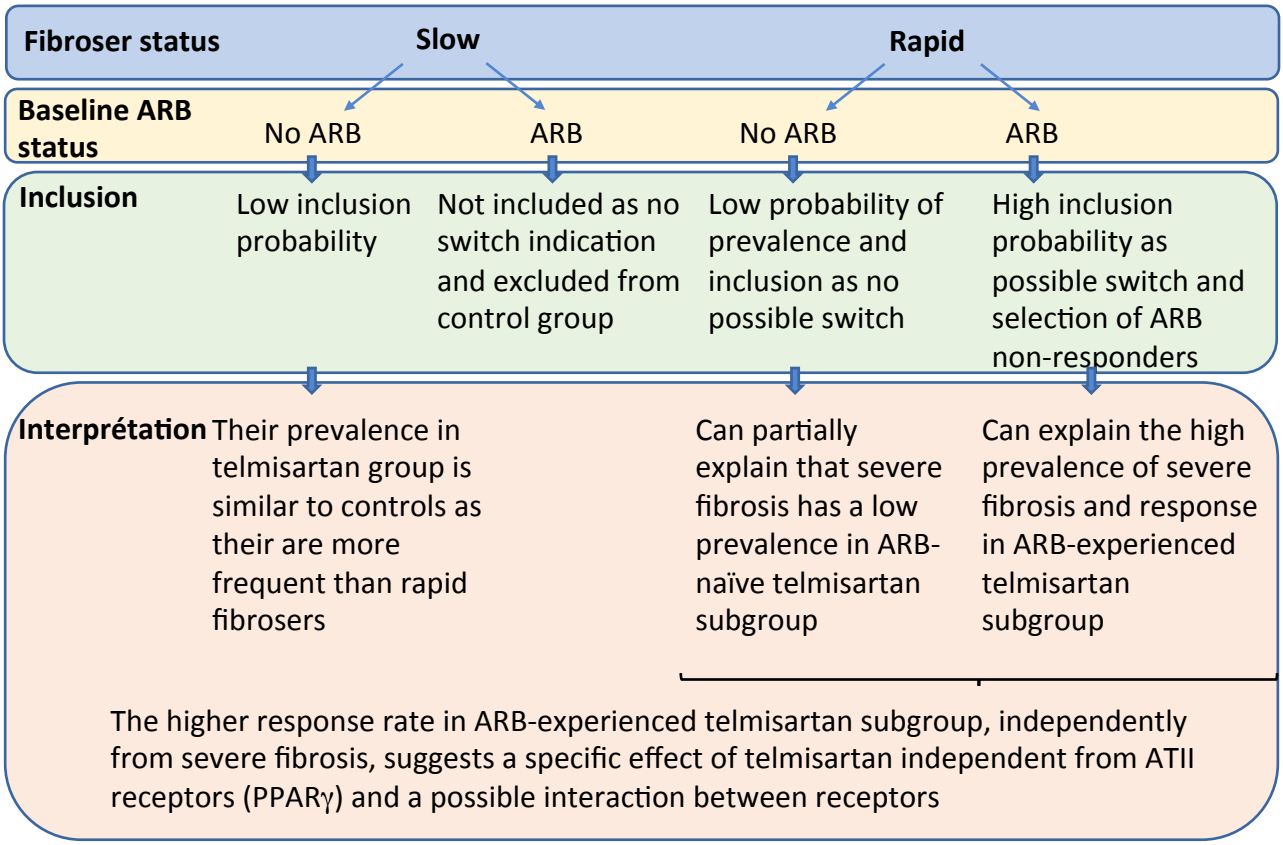

Figure S2. Main hypotheses on interrelationships between patients selection and patient results as a function of ARB status.

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LALIEU Ambroise

Effets du telmisartan sur la fibrose hépatique au cours des hépatopathies chroniques

RÉSUMÉ

Introduction : Le rôle des inhibiteurs des récepteurs de l'angiotensine II (ARB) dans le traitement de la fibrose hépatique est controversé. Le telmisartan, un ARB agoniste PPARγ, pourrait être une alternative attractive. C'est pourquoi nous avons réalisé une étude cas témoins rétrospective pour évaluer les effets du telmisartan sur la fibrose hépatique.
Méthodes : 77 patients avec hépatopathie chronique étaient éligibles et 66 ont été inclus : 37 contrôles sans ARB (avant et durant l'étude) et 29 cas recevant du telmisartan seulement durant l'étude. L'administration préalable à l'inclusion d'un ARB conventionnel (non PPARγ) était permise seulement dans le groupe telmisartan. Le critère de jugement principal (réponse) était défini par la diminution relative (delta en %) de l'élasticité hépatique, mesurée par Fibroscan, ≤ -10%.
Résultats : les caractéristiques des patients étaient, âge médian : 57 ans, hommes : 77%, NAFLD : 88% et suivi médian : 436 jours. Il n'y avait pas de différence significative entre les 2 groupes à l'inclusion sauf pour, dans le groupe telmisartan : plus de traitements (hypertension artérielle, ARB et antidiabétiques oraux), de fibrose hépatique sévère et moins d'apport ou usage d'alcool. La dose moyenne de telmisartan était de 52±19 mg/j. Le taux de réponse était, contrôles : 46% vs telmisartan : 55% (p=0,457). Les prédicteurs indépendants de la réponse étaient, à l'inclusion : apport en alcool, ARB préalable, fibrose sévère, groupe telmisartan ; et durant le suivi : durée du suivi, anti-diabétiques et delta pour ASAT et le tour de taille. Cependant, il y avait une interaction significative entre ARB préalable et telmisartan. Ainsi, le taux de réponse dépendait du statut ARB, contrôles : 46%, telmisartan ARB-naïfs : 27%, telmisartan ARB-préalable : 72% (p=0,027 vs telmisartan ARB-naïfs). Cette différence significative des taux bruts de réponse selon le statut ARB (p=0,048) n'était pas maintenue après ajustement sur les facteurs de confusion dans la population globale (p=0,435) mais était maintenue dans le groupe telmisartan (p=0,017).
Conclusion : chez les patients avec fibrose hépatique (surtout si sévère) déjà traités par ARB conventionnel, une conversion vers le telmisartan devrait être proposée.

Mots-clés : ARB, telmisartan, PPARγ, fibrose hépatique, hépatopathies chroniques

Effects of telmisartan on liver fibrosis in patients with chronic liver disease

ABSTRACT

Introduction: The role of angiotensin II receptor blocker (ARB) in the treatment of liver fibrosis is controversial. Telmisartan, an ARB PPARγ-agonist, could be an attractive alternative. Therefore, we performed a retrospective case control study evaluating the telmisartan effect on liver fibrosis.
Methods: 77 patients with chronic liver disease were eligible and 66 included: 37 controls without ARB and 29 cases receiving telmisartan only during the study. Prior conventional ARB administration was permitted only in the telmisartan group. The primary judgement criterion (response) was defined as a relative decrease in vibration controlled transient elastography (VCTE) ≤ -10%.
Results: patient characteristics were, median age: 57 years, male: 77%, NAFLD: 88% and median follow-up: 436 days. There were no significant differences between groups at baseline except for the followings, in telmisartan patients: more arterial hypertension treatment, ARB and oral antidiabetics, severe fibrosis and less alcohol intake or use. Response rate was, controls: 46% vs telmisartan: 55% (p=0.457). The independent predictors of response were, at baseline: alcohol intake, previous ARB, severe fibrosis, telmisartan group; and during follow-up: follow-up duration, anti-diabetics and variations in AST and waist circumference. However, there was a significant interaction between baseline ARB and telmisartan. Thus, the response rate depended on ARB status: controls: 46%, ARB-naïve telmisartan: 27%, ARB-experienced telmisartan: 72% (p=0.027 vs ARB-naïve telmisartan). This raw significant difference in response rate as a function of ARB status (p=0.048) was not maintained after adjustment on confusing factors in the whole population (p=0.435) but was maintained in the telmisartan group (p=0.017).
Conclusion: in patients with liver fibrosis and treated by conventional ARB, a switch to telmisartan should be proposed.

Keywords : ARB, telmisartan, PPARγ, liver fibrosis, chronic liver disease

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