IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 18, Issue 4 Ser. 13 (April. 2019), PP 54-60
www.iosrjournals.org

Interest of Fibroscan in the Evaluation and Follow-Up of Liver Fibrosis Induced By Methotrexate.

M. Azouaoui*, B. Benyachou** M. El Yousfi**, I. Mellouki**, D. Benajah**, M. El Abkari**, A. Ibrahimi**, N. Aqodad***

*** Hepatogastroenterology Department, Inezgane Prefectural Hospital Center, Morocco**
*****Hepatogastroenterology Department, HASSAN II University Hospital Center, FES, Morocco*
****Hepatogastroenterology Department, Agadir University Hospital Center, Agadir, Morocco*
Corresponding Author: M. Azouaoui

Abstract: Introduction: *Fibroscan allows non-invasive study of liver fibrosis and has recently been proposed in the follow-up of patients treated with methotrexate (MTX) in the long term for chronic inflammatory diseases. The purpose of this study is to evaluate by Fibroscan the degree of liver fibrosis induced by MTX in patients with various inflammatory diseases, comparing patients who received MTX to those naive or at the beginning of treatment.*

Materials and methods: *This is a prospective, descriptive and analytical study carried out in the gastroenterology, dermatology and rheumatology departments of Hassan II university hospital center, Fés-Morocco, from January 2011 to December 2012, including all adult patients who received different cumulative doses of MTX being explored by Fibroscan (group 1: n = 42), and compared to controls never treated or at the start of treatment (group 2: n = 43). The threshold of 7.1 was used to define a significant fibrosis> F2.*

Results: *During this period, 85 patients were included, with an average age of 44 years, with a slight female predominance of 67%. Among these patients, 31 were followed for psoriasis, 26 for other dermatological diseases, 17 for rheumatoid arthritis (RA) and 11 for chronic inflammatory bowel diseases (IBD). In group 1, the average BMI was 23.2, the average cumulative dose of MTX received was 1245 mg [105-5280 mg] for an average treatment duration of 67 weeks [13-190 weeks]. In the total population studied, the average value of Fibroscan was 4.2 KPa. Mean values of Fibroscan were not different between the two groups (4.12 VS 4.35: P> 0.05). The cumulative dose of MTX was greater than 1500 mg in 15 patients, of whom 13 were followed for PR, one for psoriasis and the other for dermatomyositis. The comparison of this group of patients with those receiving a dose <1500 mg had not shown significant differences in liver stiffness (4.17 VS 4.18: p> 0.05).*

Conclusion: *The risk of liver fibrosis during long-term treatment with MTX, regardless of indication, appears to be low and not related to cumulative dose or the duration of therapy.*

Keywords: *Fibroscan, liver fibrosis, methotrexate, chronic inflammatory diseases.*
The authors disclose no conflict of interest.

Date of Submission: 04-04-2019 Date of acceptance: 19-04-2019

I. Introduction and objectives of the study

Methotrexate (MTX) is a drug used in several disciplines as immunosuppressive and anti-inflammatory therapy, particularly in inflammatory bowel disease (IBD), rheumatoid arthritis (RA), psoriasis. However hepatic toxicity of MTX is the main constraint during the surveillance and management of these diseases [1, 2]. According to the literature, this toxicity can progress to liver fibrosis or even cirrhosis at high cumulative doses (> 1500mg) [3, 4]. Until the year 2004, the evaluation of the liver fibrosis was based on invasive means, in this case, the liver biopsy. However, this examination is burdened with morbidity and a significant mortality hence the need to develop non-invasive means to assess liver fibrosis.

Currently, a new fast and innocuous method based on the measurement of liver stiffness which is Fibroscan is available. This technique is validated in the evaluation of postviral C liver fibrosis and is being validated in other chronic liver diseases. Some studies have been shown to be effective in screening for MTX-induced liver fibrosis [5, 6]. Therefore in our study we will mainly study the results and the interest of Fibroscan in the follow-up of the patients under MTX, and secondly to compare, on the one hand, the results of Fibroscan in patients who received MXT and those who were naive or at the beginning of treatment, and on the other hand, Fibroscan results according to the cumulative dose of MTX.

II. Materials and methods

We conducted a prospective, observational study including all patients monitored, for chronic inflammatory diseases (RA, psoriasis, and IBD), receiving different doses of MTX. The study is conducted at the gastroenterology, dermatology and rheumatology departments of Hassan II University Hospital in Fes, from January 2011 to December 2012.

- **a- Inclusion of patients:** All adult patients, over the age of 18, receiving MTX and followed in all three departments were included during the study period. Failure of Fibroscan, non-cooperating patients, and patients with B and/or C viral infection were excluded from the study.
- **b- Clinical and paraclinical data:** For all patients, we specified age, sex, comorbidities, toxic habits, the indication of MTX and its therapeutic protocol (dose, route of administration, duration and cumulative dose).
  The clinical examination data were also specified: Weight, height, and BMI. All the patients had benefited from a pre-therapeutic biological assessment: complete blood count (CBC), infectious tests, serologies (hepatitis B virus, hepatitis C virus, human immunodeficiency virus, syphilis), renal and hepatic tests, serum protein electrophoresis. Abdominal ultrasound was performed in all patients before the start of treatment.
- **c- Liver stiffness measurement:** Liver stiffness measured by Fibroscan (EchoSens® Paris, France) was performed by a single-blind gastroenterologist in the gastroenterology department of the Hassan II university hospital center in Fez, in all patients before starting MTX and at precise deadlines (/ 12 months) and after a dose ≥ 1500 mg.

This rhythm of measurement of liver stiffness can be shortened in the event of a disturbance of the hepatic biological assessment and will eventually be associated with a liver biopsy. The cut-off values defining liver fibrosis (METAVIR scoring system) were established by choosing the values with the best sensitivity and specificity for each degree of fibrosis. No studies have established specific cut-off values for liver fibrosis due to MTX. The largest and most homogeneous studies included patients with chronic viral hepatitis [7-8]. We used for our study these values established by these tests [7-8] by analogy: $F \geq 2$: 7.1 kPa (sensitivity 67%, specificity 89%), $F \geq 3$: 9.5 KPa (sensitivity 84% specificity of 85%) and F4: 14.5 (sensitivity 84%, specificity 94%).

- **d- Statistical analysis:** First, we made a general description of our sample by studying the distribution of all our independent variables (sociodemographic variables, clinical variables, paraclinical variables). Subsequently, we performed a comparison between patients according to their pathologies: dermatology, rheumatology and gastroenterology, and the comparison had interested the demographic, clinical data, the cumulative dose and the duration of MTX, the biological data and the liver stiffness measurement. Then a second comparative study was performed between two groups: group 1: MTX-naive patients and group 2: patients receiving different doses of MTX, and the comparison concerned demographic, clinical, biological data and liver stiffness measurement.
  Percentage comparisons were made using the chi-square test and the Fisher test and averages using the student's test in determining the significance of each test.

Finally, an analysis was performed comparing the results of Fibroscan between patients who received a cumulative dose ≥ 1500 mg and those who received ≤ 1500 mg. A value of $p < 0.05$ was considered statistically significant. All missing values were excluded from the analyzes. The data was entered on the Excel software and analyzed on the SPSS version 20 software.

III. Results

a- Descriptive study :

Eighty-five patients were included during this study period, their mean age was 44 ± 16 [19-80 years]. The sex ratio of women/men was 2.1. Diabetes, hypertension, and obesity with a mean BMI of 36 were found in 3.5%, 1.2% and 3.5% of cases, respectively. However, the toxic habits reported were smoking and alcoholism found respectively in 9.4% and 4.7% of cases.

Among the 85 patients included in our study, 57 patients (67%) were followed in dermatology of which 54.4% were followed for psoriasis, the others (n = 26) were followed for other dermatological diseases. Seventeen patients (20%) were followed for RA and 11 patients (13%) were followed for IBD including 10 (91%) with Crohn's disease. Figure 1 summarizes the distribution of patients according to MTX indication.

All patients treated with MTX for the various pathologies received their weekly intramuscular injection treatment at a dose of 20 to 25 mg/week depending on the pathology.

In the entire population studied, the mean cumulative dose of MTX was 1245 mg [105-5280]. The dose of MTX ≥ 1500 mg was received by 16 patients (38%). Patients treated for RA received an average cumulative dose of

2582mg [800-5280 mg], while patients followed for psoriasis received an average cumulative dose of 748 mg [105-1727]. Patients treated for IBD received an average dose of 770 mg [600-1045].

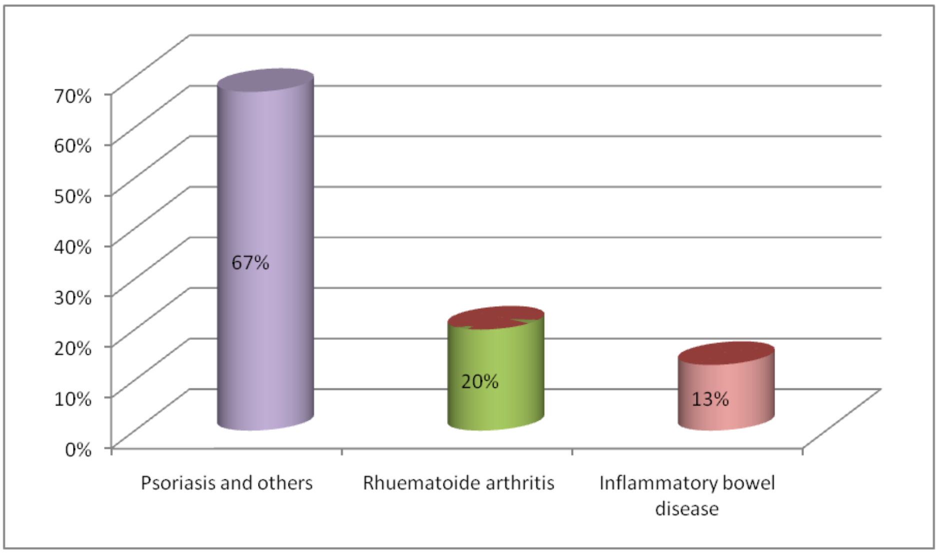

Figure 1: Distribution of patients according to MTX indication (n = 85).

The average duration of treatment received by all patients treated with MTX was 67 weeks [13-190 weeks]. The results of the biological assessment of the patients are illustrated in Table 1.

Table 1: biological data of patients

Biological examination :	Resultats (n= 85) : average
CBC:	
- **HB:**	13 g/dl
- **PLC:**	283000/mm3
- **PMN:**	4438/mm3
- **LYM:**	1741/mm3
CRP	14
Albumin	41 g/l
Renal function tests	Correcte (100%)
Liver function tests :	
- **AST:**	22 ui/l
- **ALT:**	19 ui/l
- **GGT:**	30 ui/l
- **ALP:**	98 ui/l
PT :	97%

CBC: complete blood count. HB: hemoglobin. PLC: platelet count. PMN: polymorphonuclear neutrophils. LYM: lymphocytes. CRP: C-reactive protein. AST: aspartate aminotransferase. ALT: alanine aminotransferase. GGT: gamma glutamyl-transpeptidase. ALP: alkaline phosphatase. PT: prothrombin time.

The Fibroscan values do not show any cases of significant liver fibrosis in all our patients after high doses of MTX (Table 2).

Table 2: Fibroscan results before and after receiving MTX

Elasticity	Before the start of treatment (n= 42)	Control after a dose ≥ 1500 mg (n=16)
E	5 KPa	4.4 KPa
IQR	0.8 KPa	0.5 KPa
MSR	100%	81%

E: elasticity. IQR: interquartile range. mean success rate.

b- Analytical study:

The comparative study of the entire population studied according to the pathology for which MTX was initially indicated (Table 3) shows a female predominance in the three groups, more pronounced in the case of RA with a sex ratio of 7.5 (p = 0.04), a significant difference was noted in term of cumulative dose of MTX, where a high dose was observed in patients treated for RA with an average cumulative dose of 2582 mg compared to patients treated for psoriasis (748 mg) and patients treated for IBD (770 mg): p = 0.000.

No other differences were observed between the three groups, especially there were no significant differences regarding the presence of MTX-induced liver fibrosis (p = 0.5) (Figure 2).

Table 3: Comparative study of the epidemiological, clinical and paraclinical characteristics of patients according to their pathology at inclusion:

	RA (n= 17)	Psoriasis and other (n= 57)	IBD (n= 11)	p
Age (years old)	**47**	**45**	**33**	**0.06**
Sex	**15F/2H**	**33F/23H**	**9F/2H**	**0.04**
BMI (kg/m2)	**24**	**23**	**24**	**0.7**
Cumulative dose (mg)	**2582**	**748**	**770**	**0.000**
Treatment duration (weeks)	**84**	**64**	**48**	**0.15**
Elasticity (KPa):	**4**	**5.2**	**4**	**0.5**
Biology:				
HB (g/dl):	**14**	**13**	**12**	**0.2**
WBC /mm3:	**8230**	**8126**	**8154**	**NS**
PMN /mm3:	**4438**	**4647**	**3311**	**NS**
LYM /mm3:	**1741**	**1846**	**1173**	**0.01**
PLC /mm3:	**283000**	**274000**	**335000**	**NS**
AST (ui/l):	**22**	**23**	**16**	**NS**
ALT (ui/l):	**19**	**20**	**13**	**NS**
GGT (ui/l):	**30**	**30**	**29**	**NS**
ALP (ui/l):	**98**	**101**	**100**	**0.00**
CRP (mg/l):	**14**	**15**	**10**	**NS**
PT (%):	**92**	**90**	**95**	**NS**

RA: rheumatoid arthritis. IBD: inflammatory bowel disease

HB: hemoglobin. WBC: white blood cells. PMN: polymorphonuclear neutrophils. LYM: lymphocytes. PLC: platelet count. ALP: alkaline phosphatase. CRP: C-reactive protein. PT: prothrombin time.

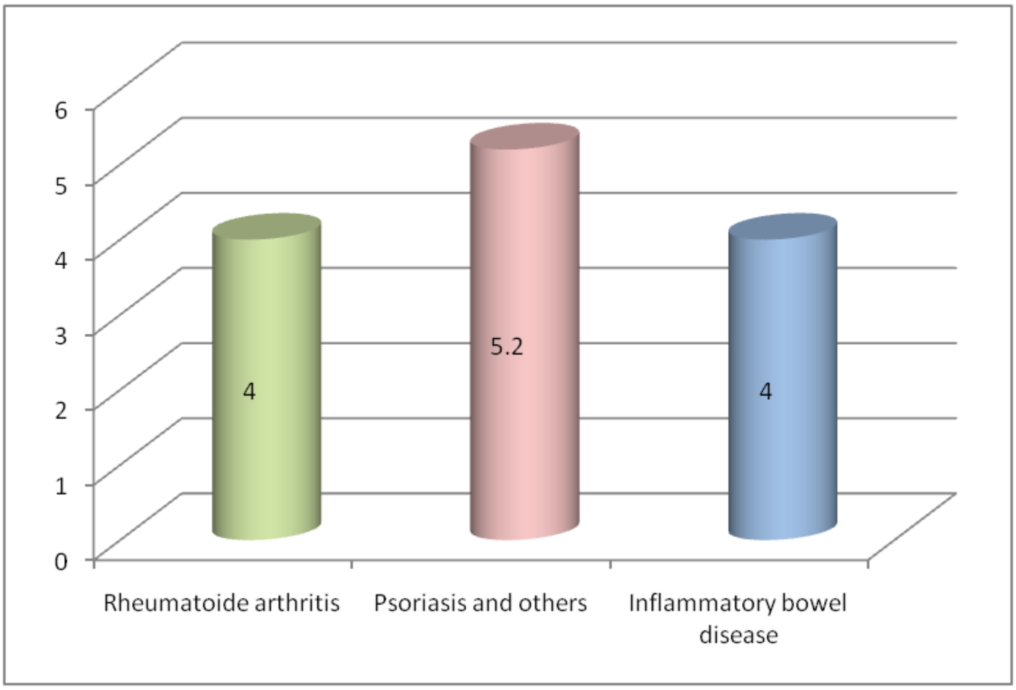

Figure 2: Liver stiffness evaluated by Fibroscan according to the pathologies (KPa): p = 0.5

The comparative study between the group of patients treated with different doses of MTX and the group of MTX-naive patients (Table 4) shows significant differences between these two groups concerning the age (p = 0.02) with a female predominance in the two groups, more marked in the group of patients treated with a sex ratio of 2.5 (p = 0.01).

Otherwise, there were no significant differences between the two groups in liver stiffness measurements (p = 0.1).

Of the 43 patients treated with MTX, only 16 (37%) received a dose ≥ 1500 mg.

The comparison of the latter group (dose ≥ 1500 mg) with the patient group receiving a dose ≤ 1500 mg did not show any significant differences except for the age when the second group had a lower age ($p = 0.03$). Liver stiffness measurement showed comparable values for both groups ($p = 0.8$) (Table 5).

Table 4: Comparative study between the group of patients treated with MTX and the group of patients who were naive to MXT.

	Group1 : treated with MTX (n=42)	Group 2 : Naive with MXT (n= 43)	p
Age (years old)	**41**	**49**	**0.02**
Sex (W/M)	**30/12**	**27/15**	**0.01**
BMI (kg/m2)	**23.6**	**23.2**	**NS**
Elasticity (KPa)	**5**	**5.7**	**0.1**
Average dose of MXT	1245 mg [105-5280].	**0 mg**	
Biology:		**12.9**	**NS**
HB (g/dl)	**12.9**	**8153**	**NS**
WBC /mm3	**8113**	**4365**	**NS**
PMN /mm3	**4491**	**4365**	**NS**
LYM /mm3	**1658**	**1855**	**NS**
PLC /mm3	**260000**	**316000**	**NS**
CRP (mg/l)	**12**	**17**	**NS**
Creatinine (mg/l)	**8.8**	**8.6**	**NS**
AST (ui/l)	**23**	**21**	**NS**
ALT (ui/l)	**24**	**22**	**NS**
GGT (ui/l)	**28**	**29**	**NS**
ALP (ui/l)	**110**	**97**	**NS**

NS : not significant. HB : hemoglobin. WBC: white blood cells. polymorphonuclear neutrophils. LYM: lymphocytes. PLC: platelet count. CRP: C-reactive protein. AST: aspartate aminotransferase. ALT: alanine aminotransferase. GGT: gamma glutamyl-transpeptidase. ALP: alkaline phosphatase.

Table 5: Comparative study of patients according to the dose received of MXT.

	Group: dose ≥1500 mg (n= 16)	Group: dose ≤1500 mg (n=42)	p
Age (years old):	**47**	**38**	**0.03**
Sex (W/M):	**12F/4H**	**33F/9H**	**NS**
BMI (kg/m2)	**25**	**23**	**NS**
Elasticity (KPa)	**4.5**	**4.4**	**NS**
Biology:			
HB (g/dl)	**14**	**12.8**	**NS**
WBC /mm3	**8290**	**8099**	**NS**
PMN e/mm3	**5280**	**4386**	**NS**
LYM /mm3	**1453**	**1676**	**NS**
PLC /mm3	**283000**	**262000**	**NS**
AST (ui/l)	**34**	**22**	**NS**
ALT (ui/l)	**22**	**14**	**NS**
GGT (ui/l)	**21**	**23**	**NS**
ALP (ui/l)	**100**	**96**	**NS**

NS : not significant. HB : hemoglobin. WBC: white blood cells. polymorphonuclear neutrophils. LYM: lymphocytes. PLC: platelet count. AST: aspartate aminotransferase. ALT: alanine aminotransferase. GGT: gamma glutamyl-transpeptidase. ALP: alkaline phosphatase.

IV. Discussion

The relationship between MTX-based therapy and the development of liver fibrosis was reported in several studies [16, 8, 17, 18]. The pathophysiology of the hepatotoxicity of MTX is poorly understood and the liver response to inflammation is liver fibrosis via stellate cells of the liver.Whatever the mechanism of this hepatotoxicity, it also depends on associated factors such as alcohol consumption or insulin resistance that activate the stellate cells of the liver [26]. The evaluation of this liver fibrosis was based until recently on the liver biopsy which remains the gold standard in this case. However, it presents several complications and limits to its use [19, 20], hence the recent tendency to replace it with several non-invasive methods including Fibroscan. Several studies have shown the existence of a significant correlation between measures of liver stiffness by Fibroscan and the degree of liver fibrosis. The optimal cut-off values for significant fibrosis ($F \geq 2$) are variable depending on the underlying liver disease. Therefore values reported in patients with hepatitis C virus were classified between 7.1 and 8.7 KPa [20,21], those reported in patients with NASH to define the same degree of fibrosis were 6.8 KPa [22, 23].

In our study we used by analogy the same significant fibrosis thresholds reported in case of chronic hepatitis C.

The comparative study between the three groups of patients (PR, psoriasis, and IBD), showed a significant difference in cumulative dose of MTX ($p = 0.00$), where a higher dose was observed in patients treated for RA. This result was similar to other findings reported by other studies [27, 28]. No cases of liver fibrosis have been found in our patients. There was also no significant difference in liver stiffness measurement between the three groups of patients, where the mean stiffness was 4.5 KPa ($p = 0.5$), even after a cumulative dose greater than 1500 mg, which is in favor of absence of MTX-induced liver fibrosis. This result was also reported by other studies [27, 5, 29].

The study by Almudena Barbero-Villares et al [27] compared the results of 53 patients, of whom 17 were followed for RA, 18 for IBD and 18 for psoriasis, and concluded that there was no significant difference between the three groups of patients regarding liver stiffness with an average of 6.1KPa, after an average cumulative dose of 1560 mg. The same study had demonstrated significant liver fibrosis ≥ F3 in four patients and had demonstrated that the latter was secondary to alcohol abuse, further enhancing the safety of MTX. The study of D. Laharie et al. [5] including 62 patients treated with a high dose of MTX (mean: 2899 +/- 260 mg) for Crohn's disease (CD), concluded that liver fibrosis was rare in CD treated with high doses of MXT, and that Fibroscan could be reliably used as a first line for the evaluation of liver fibrosis in these MTX-treated patients regardless of disease activity and has been shown to be useful in avoiding biopsy in most patients. Our study included 10 patients followed for CD, with a mean cumulative MXT dose of 770 mg [600-1045]. This number of patients appears to be lower than that reported by other studies, and this may be related to the recent inclusion of these patients in the study. The study of liver stiffness in our Crohn's patients had shown no case of liver fibrosis. In another study of Almudena Barbero-Villares [30] including 46 patients, 31 patients had CD, 13 ulcerative colitis, and 2 indeterminate colitis. The mean cumulative dose of MTX was 1242 ± 1349 mg, with a mean duration of treatment of 21 ± 24 months. The mean value of liver stiffness was 4.7 ± 6.9 kPa. This study showed that there was no difference in liver stiffness, by sex, age, type of IBD, or cumulative dose of MTX.

In our study, the comparison of patients treated with MXT and the group of patients naïve for MTX, showed no case of liver fibrosis in the group of patients treated, and no significant difference in terms of liver stiffness measurement (5 vs. 5.7 KPa). Our results were consistent with those reported by D. Laharie et al. [5] where there was no significant difference between patients in group 1 (high dose) and group 2 (naive).

Several studies have shown that alcohol consumption, obesity and diabetes are associated with the risk of liver fibrosis in patients treated with MTX. Therefore, liver fibrosis associated with methotrexate could be due to associated factors instead of methotrexate itself [26]. This result was also reported in another study [31], including 518 patients of which 44 patients (8.5%) had Fibroscan results suggestive of severe liver fibrosis, and whose multivariate analysis had shown that neither the high cumulative dose, nor the long duration of treatment were associated with these high elasticity results in these patients. The study found other factors associated with this liver fibrosis, BMI ≥28kg / m2 and alcohol consumption, and concluded that severe liver fibrosis was a rare event in patients treated with MTX, and was probably unrelated to the cumulative dose, suggesting that patients with risk factors for liver disease should be closely monitored with non-invasive methods before and during treatment with MTX. Our comparative study according to the cumulative doses (≥1500 mg vs ≤100 mg), showed no significant difference between the two groups in particular in term of liver stiffness (4.5 vs 4.4 KPa), results similar to the results of previous studies [26-31].

V. Conclusion

The results of our prospective study, despite its small size, suggest that MTX does not lead to the development of liver fibrosis, regardless of the underlying pathology, dose and duration of MTX.

References

[1]. Tolman KG, Clegg DO, Lee RG, Ward JR. Methotrexate and the liver. J Rheumatol.1985;12(suppl):29-34.

[2]. van de Kerkhof PCM, Hoefnagels WH, van Haelst JG, Mali JW. Methotrexate maintenance herapy and liver damage in psoriasis. Clin Exp Dermatol. 1985;10:194-200.

[3]. Kremer JM, Alarcon GS, LightfootRWJr, et al, for the American College of Rheumatology. Methotrexate for rheumatoid arthritis: suggested guidelines for monitoring liver toxicity. Arthritis Rheum. 1994;37:316-328.

[4]. Erickson AR, Reddy V, Vogelgesang SA, West SG. Usefulness of the American College of Rheumatology recommendations for liver biopsy in methotrexate-treated rheumatoid arthritis patients. Arthritis Rheum. 1995;38:1115-1119.

[5]. Laharie D, Zerbib F, Adhoute X, Boue-Lahorgue X, Foucher J,Castera L, Rullier A, et al. Diagnosis of liver fibrosis by transient elastography (FibroScan) and noninvasive methods in Crohn's disease patients treated with methotrexate. Aliment Pharmacol Ther 2006;23:1621—8.

[6]. Kremer JM, Lee JK. The safety and efficacy of the use of methotrexate in long-term therapy for rheumatoid arthritis. Arthritis Rheum 1986;29:822—31.

[7]. Almudena Barbero-Villares et al. Evaluation of liver fibrosis by transient elastography in methotrexate treated patients. MEDCLI-1835; No. of Pages 3. December 2010
[8]. Castera L, Vergniol J, Foucher J, Le Bail B, Chanteloup E, Haaser M, et al. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. Gastroenterology.2005 Feb; 128(2): 343–50.
[9]. Kazemi F, Kettaneh A, N'kontchou G, Pinto E, Ganne-Carrie N, Trinchet JC, et al. Liver stiffness measurements selects patients with cirrhosis at risk of bearing large esophageal varices. J Hepatol 2006;45: 230-235.36
[10]. Vizzutti F, Arena U, Romanelli RG, Rega L, Foschi M, Colagrande S, et al. Liver stiffness measurement predicts severe portal hypertension in patients with HCV-related cirrhosis. Hepatology 2007;45:1290–1297.
[11]. Castéra et al. Early detection in routine clinical practice of cirrhosis and oesophageal varices in chronic hepatitis C: Comparison of transit elastography (FibroScan) with standard laboratory tests and non-invasive scores. Journal of Hepatology 50 (2009) 59-68
[12]. Castera L. intéret de l'élastométrie (FibroScan) pour l'évaluation non invasive de la fibrose hépatique. Gastroenterol Clin Biol 2007;31: 524-530
[13]. Castera L, Xavier Forns, Alfredo Alberti. Non-invasive evaluation of liver fibrosis using transient elastography. Journal of Hepatology 48 (2008) 835- 847
[14]. C. Bureau et al. Transient elastography accurately predicts presence of significant portal hypertension in patients with chronic liver disease.Alimentary Pharmacology et Therapeutics 27, 1261-1268
[15]. Don C. Rockey. Non-invasive assessment of liver fibrosis and portal hypertension with transient elastography. Gastroenterology 2008;134:814
[16]. Anto´n MD, Rosello´ E, Go´mez F, Paredes JM, Lo´pez A, Moreno-Osset E. Hepatic steatosis in chronic hepatitis C: study of risk factors and relationship with the fibrosis stage. Med Clin (Barc). 2009;132:574–9.
[17]. Bridges SL, Alarcon JM, Koopman WJ. Methotrexate-induced liver abnormalities in rheumatoid arthritis. J Rheumatology 1989; 16: 1180–3.
[18]. Rau R, Karger T, Herborn G, Frenzel H. Liver biopsy findings in patients with rheumatoid arthritis undergoing longterm treatment with methotrexate. J Rheumatol 1989; 16: 489–93.
[19]. Cadranel JF, Rufat P, Degos F. Practices of liver biopsy in France: results of a prospective nationwide survey. For the Group of Epidemiology of the French Association for the Study of Liver. Hepatology. 2000; 32:477–481.
[20]. Bedossa P. Sampling variability of liver fibrosis in chronic hepatitis C. Hepatology. 2003; 38:1449–1457.
[21]. Mendoza J, Go´mez-Domı´nguez E, Moreno-Otero R. Transient elastography (Fibroscan), a new non-invasive method to evaluate hepatic fibrosis. Med Clin (Barc). 2006;126:220–2.
[22]. Lupsor M et al. (2010). Performance of unidimensional transient elastography in staging non-alcoholic steatohepatitis. Journal of Gastrointestinal and Liver Diseases. Volume 19, No. 1, pp. 53-60.
[23]. Abenavoli L, Beaugrand M.Transient elastography in non-alcoholic fatty liver disease. Ann Hepatol. 2012 Mar-Apr; 11(2):172-8
[24]. Roulot D, Czernichow S, Le Clésiau H, Costes JL, Vergnaud AC, Beaugrand M. Liver stiffness values in apparently healthy subjects: influence of gender and metabolic syndrome. J Hepatol. 2008 Apr; 48(4):606-13.
[25]. Roulot D, Costes JL, Buyck JF, Warzocha U, Gambier N, Czernichow S, Le Clesiau H, Beaugrand M. Transient elastography as a screening tool for liver fibrosis and cirrhosis in a community-based population aged over 45 years. Gut. 2011 Jul;60(7):977-84.
[26]. D. Laharie et al.The liver and methotrexate. Gastroentérologie Clinique et Biologique. Volume 32, n° 2 pages 134-142 (février 2008)
[27]. Almudena Barbero-Villares a, Jorge Mendoza a, Marı´aTrapero-Marugan a, Isidoro Gonzalez-Alvaro b, Esteban Daude´n c, Javier P. Gisbert a, Ricardo Moreno-Otero a,* Evaluation of liver fibrosis by transient elastography in methotrexate treated patients Med Clin (Barc). 2011
[28]. Sung-Hoon Park, Jung-Yoon Choe∗, Seong-Kyu Kim. Assessment of liver fibrosis by transient elastography in rheumatoid arthritis patients treated with methotrexate. Joint BoneSpine 77 (2010) 588–592
[29]. Berends MA, Snoek J, De Jong EM, Van Krieken JH, De Knegt RJ, Van Oijen MG et al. Biochemical and biophysical assessment of MTX-induced liver fibrosis in psoriasis patients: Fibrotest predicts the presence and Fibroscan predicts the absence of significant liver fibrosis. Liver Int. 2007; 27:639–45.
[30]. Barbero-Villares A et al. Evaluation of liver fibrosis by transient elastography (Fibroscan®) in patients with inflammatory bowel disease treated with methotrexate: a multicentric trial. Scand J Gastroenterol. 2012 May;47(5):575-9.
[31]. Laharie D et al. Assessment of liver fibrosis with transient elastography and FibroTest in patients treated with methotrexate for chronic inflammatory diseases: a case-control study. J Hepatol. 2010 Dec;53(6):1035-40.

M. Azouaoui. " Interest of Fibroscan in the Evaluation and Follow-Up of Liver Fibrosis Induced By Methotrexate." IOSR Journal of Dental and Medical Sciences (IOSR-JDMS), vol. 18, no. 4, 2019, pp 54-60.