
Dans notre cas, l’hépatite auto-immune a été confirmée par l’examen histologique, la positivité à distance des anticorps, l’apparition d’une hypergammaglobulinémie, ainsi que le terrain auto-immun connu du fait de sa thyroïdite d’Hashimoto. La possibilité d’une hépatite immuno-allergique est difficile à éliminer mais la réaggravation de l’hépatite sans réintroduction du médicament ainsi que la positivité des anticorps nous conforte sur notre diagnostic.

Le mécanisme de la toxicité de l’imatinib n’est pas connu, un mécanisme d’hypersensibilité a été suggéré [5,6], la production de métabolites nocifs ne peut être exclu. En effet, ce médicament est métabolisé par le foie par le système CYP3A4. L’imputabilité de l’imatinib a été renforcée par des tentatives de réinsertion du médicament, déclenchant une rechute de l’hépatite auto-immune.

**Conflits d’intérêts**

Aucun.

**Références**


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Disponible sur Internet le 17 septembre 2009

**Metformin plus pentoxifylline versus prescriptive diet in non-alcoholic steatohepatitis (NASH): A randomized controlled pilot trial**

**Metformine plus pentoxifylline versus mesures hygiénodiététiques dans la stéatohépatite métabolique (NASH): essai pilote randomisé contrôlé**

There is no definitive treatment for non-alcoholic steatohepatitis (NASH) [1]. Preliminary studies have suggested that metformin, an insulin-sensitizing agent, leads to improvement in alanine aminotransferase (ALT) levels and, less frequently, in liver histology in patients with NASH [2]. Pentoxifylline suppresses tumor necrosis factor (TNF)-alpha production, at least in vitro [3], and decreases serum ALT levels and liver inflammation in a methionine choline-deficient (MCD) model of NASH [4] and in a NASH model induced by high-fat diet [5] but not in a choline-deficient diet model [6] in mice. Indeed, several studies have shown that pentoxifylline has a beneficial effect on ALT levels and histological lesions in patients with NASH [7,8]. The aim of this randomised, multicenter, open controlled pilot trial was to compare 48 weeks of treatment with metformin plus pentoxifylline versus a dietetic regimen alone in non-diabetic adults with NASH, with a special focus on liver histology.

Eligibility criteria for the study were: [1] 18—70-year-old non-alcoholic patients with persistently elevated serum ALT levels, [2] liver biopsy performed no more than 12 months before inclusion showing histological features of NASH. Patients with known diabetes were excluded. The study was approved by the appropriate ethical committees.

After basal assessment, all patients received 2 hours of nutritional counselling by an experienced dietician. They were then randomly assigned to treatment according to the two-arms protocol: counselling by the dietician alone (arm 1) or metformin treatment at a daily maximum dose of 1500 mg (increasing doses from 500 mg/day for 10 days to 1000 mg/day for 10 days and then a full dose of 1500 mg/day) associated with pentoxifylline (4 mg, three times/day) for 48 weeks (arm 2) and dietetic counselling. No specific exercise was proposed. Both patients and investigators were not blind to treatment.

Treatment was provided for 48 weeks with biochemical and clinical control visits every 3 months. A liver biopsy was performed at week 48. Compliance was tested by pill counts in subjects on metformin and pentoxifylline.

The primary endpoint was improvement in liver histology. All paired liver biopsies (baseline and without knowledge of the treatment arm). Fibrosis stage
(0–4), percentage and grade (0–3) of steatosis, lobular inflammation (0–3), hepatocellular ballooning (0–2), NAFLD activity score (NAS) and histological iron deposits (0–4 according to Searle) were evaluated semi-quantitatively. The secondary endpoints were the main clinical data including weight and body mass index (BMI), and biochemical parameters (ALT, aspartate aminotransferase [AST], gamma glutamyltransferase [GGT], Homa score, total cholesterol and triglycerides) and the tolerability. The Kruskal-Wallis statistical analysis of variance tests were used to compare values between the two arms. The Wilcoxon matched pairs test was used for comparison with treatment arms. For categorical parameters, the percentage of distribution was analyzed with the Chi² test. Differences at p less than 0.05 were considered to be statistically significant.

Nineteen patients from five French centers were included. Demographic characteristics (age, gender, BMI) were not significantly different between the two arms (Table 1). All patients had NAS greater or equal to four at baseline, with NAS greater or equal to five for 17 patients. None of the histological parameters was significantly different among the two groups. A statistically significant difference was observed between baseline and week 48 for weight loss (p = 0.023) in the metformin plus pentoxifylline group. No difference was observed in BMI or biochemical parameters, although ALT tended to decrease (p = 0.07). In the diet group, there was no difference between baseline and week 48 for the different clinical and biochemical parameters. Five paired biopsies in the treated group and seven in the diet group were available, and no statistical difference in histological parameters was observed between the two groups although there was a tendency for higher NAS to decrease in the metformin plus pentoxifylline group. Two patients treated with metformin plus pentoxifylline stopped the treatment in the first months of therapy due to adverse events (nausea and diarrhea). In this group, the main adverse events were fatigue in three patients (30%), diarrhea in four (40%), arthralgia and myalgia in three patients (30%), insomnia in one (10%) and nausea in one (10%). In patients following the diet, the main adverse events were fatigue in three patients (30%), diarrhea in four (40%), arthralgia and myalgia in two (22.2%), depression in two patients (22.2%), insomnia in one (11.1%) and hypotension in two patients (22.2%).

**Discussion**

This study fails to demonstrate that long term metformin plus pentoxifylline treatment improves clinical, biochemical and histological parameters in patients with NASH. These results are different from those observed in other studies. Several trials including a few patients had shown that metformin at the same dose and duration of treatment significantly decreases weight, BMI and ALT levels [2,10–14]. A histological improvement was also observed with a weight loss of at least 6 kg. Pilot trials [7,15,16] have also suggested that pentoxifylline decreased transaminase levels in patients with NASH, associated with histological improvement in two studies [7,16]. Unfortunately, in our study, we

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**Table 1 Evolution of clinical, biochemical and histological parameters in the two groups of patients.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Metformin plus pentoxifylline (N = 10)</th>
<th>Diet (N = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Week 48</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80.5 ± 11.1</td>
<td>79.0 ± 13.9</td>
</tr>
<tr>
<td>Body mass index</td>
<td>29.9 ± 4.6</td>
<td>30.0 ± 5.0</td>
</tr>
<tr>
<td>Alanine aminotransferase (ULN)</td>
<td>2.4 ± 1.0</td>
<td>1.8 ± 0.9</td>
</tr>
<tr>
<td>Aspartate aminotransferase (ULN)</td>
<td>1.8 ± 1.1</td>
<td>1.2 ± 0.4</td>
</tr>
<tr>
<td>Gamma glutamyltransferase (ULN)</td>
<td>3.0 ± 2.6</td>
<td>5.0 ± 6.4</td>
</tr>
<tr>
<td>Homa score</td>
<td>4.3 ± 4.1</td>
<td>2.9 ± 2.1</td>
</tr>
<tr>
<td>Total cholesterol (g/L)</td>
<td>2.4 ± 0.4</td>
<td>2.2 ± 0.6</td>
</tr>
<tr>
<td>Triglycerides (g/L)</td>
<td>2.2 ± 1.0</td>
<td>1.7 ± 0.5</td>
</tr>
</tbody>
</table>

**Histological lesions**

<table>
<thead>
<tr>
<th>Steatosis (%)</th>
<th>Metformin plus pentoxifylline</th>
<th>Diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>5–33</td>
<td>0</td>
<td>22</td>
</tr>
<tr>
<td>33–66</td>
<td>40</td>
<td>11</td>
</tr>
<tr>
<td>&gt; 66</td>
<td>50</td>
<td>67</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Iron (%)</th>
<th>Metformin plus pentoxifylline</th>
<th>Diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>Mild</td>
<td>30</td>
<td>22</td>
</tr>
<tr>
<td>Moderate</td>
<td>20</td>
<td>67</td>
</tr>
<tr>
<td>Severe</td>
<td>10</td>
<td>11</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NAFLD activity score (mean ± SD)</th>
<th>Metformin plus pentoxifylline</th>
<th>Diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.8 ± 1.9</td>
<td>3.8 ± 2.4</td>
<td>5.6 ± 0.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fibrosis stage (mean ± SD)</th>
<th>Metformin plus pentoxifylline</th>
<th>Diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.7 ± 1.1</td>
<td>2.0 ± 1.0</td>
<td>2.0 ± 1.1</td>
</tr>
</tbody>
</table>

ULN: upper limit of normal; NAFLD: non-alcoholic fatty liver disease. * p = 0.023.
did not observe any significant decrease in BMI, ALT levels or changes in histological parameters in spite of weight loss.

Indeed, in our study, the number of patients was lower than planned probably because of inclusion criteria. We excluded patients with diabetes usually associated with severe NASH. However, the difference in terms of response to therapy could be due to patient characteristics at entry, especially because of the lack of severe obesity and diabetes in patients, the mean NAS and low fibrosis stage at baseline, and also not enough weight loss to induce biochemical and histological changes. Indeed, the combination therapy did not seem to increase the efficacy of each drug and was poorly tolerated. Numerous side effects were observed in the treated group compared to previous studies, especially digestive disorders and two patients stopped the treatment in the first months of therapy.

In conclusion, our results do not support the use of this combination therapy in the treatment of mild or moderate histologically proven NASH. Other approaches seem to be more promising for the future such as thiazolidinedione or antagonists of the cannabinoids receptor type I.

Conflicts of interests

None.

References


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Available online 30 July 2009

doi:10.1016/j.gcb.2009.05.010

Acanthosis nigricans révélateur d’un adénocarcinome de la vésicule biliaire

Adenocarcinoma of gallbladder revealed by acanthosis nigricans

L’acanthosis nigricans est une éruption cutanée généralement observée dans le cadre du syndrome...