
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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meters, although ALT tended to decrease (p = 0.023). In the metformin plus pentoxifylline group, there was no difference between baseline and week 48 for weight loss (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 patients (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

(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 one patient (11.1%), 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%).

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

<table>
<thead>
<tr>
<th></th>
<th>Metformin plus pentoxifylline (N = 10)</th>
<th>Diet (N = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td><strong>Week 48</strong></td>
<td><strong>Baseline</strong></td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>80.5 ± 11.1</td>
<td>79.0 ± 13.9*</td>
</tr>
<tr>
<td><strong>Body mass index</strong></td>
<td>29.9 ± 4.6</td>
<td>30.0 ± 5.0</td>
</tr>
<tr>
<td><strong>Alanine aminotransferase (ULN)</strong></td>
<td>2.4 ± 1.0</td>
<td>1.8 ± 0.9</td>
</tr>
<tr>
<td><strong>Aspartate aminotransferase (ULN)</strong></td>
<td>1.8 ± 1.1</td>
<td>1.2 ± 0.4</td>
</tr>
<tr>
<td><strong>Gamma glutamyltransferase (ULN)</strong></td>
<td>3.0 ± 2.6</td>
<td>5.0 ± 6.4</td>
</tr>
<tr>
<td><strong>Homa score</strong></td>
<td>4.3 ± 4.1</td>
<td>2.9 ± 2.1</td>
</tr>
<tr>
<td><strong>Total cholesterol (g/L)</strong></td>
<td>2.4 ± 0.4</td>
<td>2.2 ± 0.6</td>
</tr>
<tr>
<td><strong>Triglycerides (g/L)</strong></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 (N = 10)</th>
<th>Diet (N = 9)</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>
<tr>
<td><strong>Iron (%)</strong></td>
<td></td>
<td></td>
</tr>
<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>
<tr>
<td><strong>NAFLD activity score (mean ± SD)</strong></td>
<td>4.8 ± 1.9</td>
<td>3.8 ± 2.4</td>
</tr>
<tr>
<td><strong>Fibrosis stage (mean ± SD)</strong></td>
<td>1.7 ± 1.1</td>
<td>2.0 ± 1.0</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 cannabinoid receptors type 1.

**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...