Dans les deux cas publiés, il s’agit de femmes jeunes, 17 et 18 ans, ayant présenté une hépatite deux semaines et 18 mois après le début du traitement. Dans les deux cas, on retrouve une faible négativité des anticorps antimuscles lisses, anti-LKM1 et antinucléaires. De même, la ponction-biopsie hépatique n’a été effectuée qu’à distance (à un mois), mettant en évidence les mêmes anomalies histologiques.

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, 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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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 week 48) were reviewed by a single senior liver pathologist (NS), on hematoxylin-eosin-saffron and red Sirius stained sections, according to the scoring system proposed by Kleiner et al. [9] and without knowledge of the treatment arm. Fibrosis stage
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></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></th>
<th>Steatosis (%)</th>
<th>Iron (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 5</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>5–33</td>
<td>Mild</td>
</tr>
<tr>
<td></td>
<td>33–66</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>&gt; 66</td>
<td>Severe</td>
</tr>
<tr>
<td>NAFLD activity score (mean ± SD)</td>
<td>4.8 ± 1.9</td>
<td>3.8 ± 2.4</td>
</tr>
<tr>
<td>Fibrosis stage (mean ± SD)</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.

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...
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 receptor type I.

Conflicts of interests

None.

References


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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...