An Open Study of Modafinil for the Treatment of Daytime Somnolence and Fatigue in Primary Biliary Cirrhosis

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Running Title: Modafinil in PBC

Key Words: liver cirrhosis, biliary; quality of life; fatigue; symptom; sleep

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Summary

Background & Aim: Fatigue is a debilitating symptom which frequently impairs the quality of life of patients with primary biliary cirrhosis (PBC), and which is unresponsive to currently available treatments. Although the mechanisms underpinning fatigue in PBC remain unclear there is an emerging consensus that CNS mechanisms play a key role. It has recently been shown that there is a strong association between abnormalities in sleep regulation, in particular excessive daytime somnolence, and fatigue severity in PBC. The CNS-acting drug modafinil has an established role in the treatment of excessive daytime somnolence in non-liver disease states. In this open label study we set out to explore the responses of PBC patients suffering from significant daytime somnolence and associated fatigue to modafinil therapy.

Methods: All patients in the series (n=21) underwent daytime somnolence assessment using the Epworth Sleepiness Scale (ESS) and PBC symptom assessment using the PBC-40, a multi-domain, disease specific, psychometrically robust quality of life measure. Modafinil was started at a dose of 100mg per day and was titrated according to tolerability and response. Patients underwent repeat ESS and PBC-40 assessment after 2 months of treatment.

Results: Significant improvement was seen in ESS scores with Modafinil therapy (15.0 ± 3.3 v 8.0 ± 5.6, p<0.0005 (intention to treat (ITT) analysis)). An equally significant improvement in fatigue severity was also seen (PBC-40 Fatigue domain score 46.1 ± 6.2 v 33.5 ± 12.2, p<0.0001 (ITT analysis).

Conclusions: Open label Modafinil therapy was associated, where tolerated by patients, with improvement in excessive daytime somnolence and associated fatigue in PBC. Further study in placebo-controlled trials is warranted.
Background

Primary biliary cirrhosis (PBC) is a chronic cholestatic liver disease (1). The condition, which affects up to 1 in 700 women over the age of 40 in some western European populations, is characterised by the development, in up to half of patients, of profound fatigue (2-5). Studies performed both in PBC patients and in animal models of cholestasis have suggested that central nervous system processes, driven by a combination of cholestasis and inflammation, play a key role in the development of fatigue (6-8). Although our state of knowledge regarding potential mechanisms for the pathogenesis of fatigue in PBC has improved in recent years this has not, as yet, been reflected in significant improvements in the therapeutic options available for clinicians treating patients with this often disabling symptom (9).

There is now emerging evidence to suggest that fatigue in PBC is associated with abnormality in sleep in general and with excessive daytime sleepiness in particular (2,10). PBC patients sleep significantly more during the daytime than matched controls as assessed using both objective measures of sleep and subjective measures of perception of sleep (10). The degree of daytime sleep assessed using both approaches correlates both with general impairment of quality of life and with severity of fatigue. In light of the degree of daytime somnolence experienced by PBC patients, and the association between daytime somnolence and fatigue, we treated a series of PBC patients with excessive daytime somnolence with modafinil, a CNS-active agent effective for the treatment of daytime somnolence in the context of narcolepsy (11,12) and obstructive sleep apnea (13) and in excessive sleepiness in shift-work sleep disorder (14). In a recent case series of 5 PBC patients receiving modafinil therapy improvement in fatigue severity was reported, but not quantified (15). Here we report on the tolerability of modafinil in PBC patients and quantify its effects on daytime somnolence and fatigue in an open label study.
Subjects & Methods

Study Participants & Protocol

The study participants were a series of 21 patients with definite or probable PBC, diagnosed using established criteria (16), who suffered from clinically significant daytime somnolence seen in our specialist PBC Service between September 2005 and February 2006. PBC patients were considered to be suitable for modafinil therapy if they had an Epworth Sleepiness Scale (ESS) score of 10 or greater in the absence of clinical features suggestive of obstructive sleep apnea. The ESS is a fully-validated and psychometrically robust tool for the assessment of daytime somnolence (17), which has previously been used in the assessment of excessive daytime somnolence in PBC patients (10). Clinically significant daytime somnolence is considered as being present when ESS scores exceed 10 (17). Patients were excluded from modafinil therapy if they had a history of hypertension or other conditions recognised as contra-indicating modafinil therapy, had a history of, or features on investigation which were suggestive of, either other liver disease processes or inter-current conditions which are themselves associated with excessive daytime somnolence. Patients were also excluded from modafinil therapy if they were receiving other medications recognised as interacting with modafinil or which were associated with sleep disturbance. The clinical details of the patients in the series are outlined in Table 1. None of the patients in this case series had advanced liver disease and none had clinical features suggestive of the presence of hepatic encephalopathy.

All subjects underwent a full symptom assessment prior to commencement and after 2 months of treatment. Patients underwent interim assessment after 4 weeks therapy at which issues relating to the tolerability of modafinil therapy were addressed and at the point of discontinuation of treatment in patients unable to tolerate modafinil. Assessment tools were the ESS and the PBC-40, a recently described disease specific health-related quality of life (HRQOL) measure developed and validated for use exclusively in PBC (18,19). The PBC-40 consists of 5 symptom domains relating to “fatigue”, “itch”, “cognitive” symptoms, “social and emotional” symptoms and “other symptoms”. The psychometric properties of the PBC-40 have been previously been described in detail (18). All patients were commenced on modafinil at a dose of 100mg per day. The dose was subsequently titrated according to both response and tolerability up to a maximum of 200mg/day.
Statistical Analysis

Symptom severity scores prior to treatment and at 2 months following the institution of treatment were compared using Student’s t-test on an “intention to treat” (ITT) and per protocol basis. Bonferroni’s correction was applied to correct for multiple testing of the domains of the PBC-40. Percentages of patients experiencing symptoms prior to therapy and at two months following the institution of therapy were compared using the Chi-squared test.
Results

All patients in the series initially received 100 mg per day of modafinil. The dose was increased at one month of treatment to 200 mg according to tolerability and response. Patients unable to tolerate 100 mg initially halved the dose to 50 mg per day and, if still unable to tolerate it, discontinued treatment. Of the 21 participants, 14 were able to tolerate the treatment for the full 2 month period. The mean dose amongst these recipients was 115 mg per day. All 7 of the recipients who were unable to tolerate treatment suffered from significant headaches which resolved immediately on discontinuation of the treatment. In none of these patients was headache associated with significant increase in blood pressure. Amongst the patients not experiencing headaches and who took the drug for the full 2 months no other side-effects were identified.

Reduction was seen in degree of daytime somnolence (as assessed using the ESS) with modafinil treatment when analysed on both a per protocol basis (Figure 1) and on an intention to treat basis (mean ESS pre-treatment 15.0 ± 3.3 (possible value range 0-24) v post-treatment 7.9 ± 5.6; p<0.0005). Of the 14 PBC patients able to tolerate modafinil 12 (86%) demonstrated improvement in their ESS score (range of improvement 18-94%). 11/14 (79%) of the patients able to tolerate to modafinil (11/21 (52%) of the whole cohort) had a final ESS score of <10 (the established criterion for significant daytime somnolence and the ESS criterion for modafinil therapy in this series). 17 of the patients receiving modafinil in this series had severe fatigue at the outset of treatment (defined as a PBC-40 fatigue domain score >40) and the remaining 4 had moderate fatigue (PBC-40 fatigue domain score 29-39). Modafinil therapy was associated with a reduction in fatigue severity when analysed on both a per protocol basis (Figure 2, Table 2) and on an intention to treat basis (mean PBC-40 Fatigue domain score pre-treatment 46.1 ± 6.2 (possible value range 11-55) v post-treatment 33.5 ± 12.2; p<0.0001) (Table 2). Of the 11 patients able to tolerate modafinil who had severe fatigue at the outset of the study (the remaining 6 subjects with severe fatigue at study outset were unable to tolerate modafinil) only 1 still reported severe fatigue after 2 months of modafinil therapy (p=0.001). More modest, but still statistically significant improvement was seen in PBC-40 cognitive domain scores with Modafinil therapy when analysed on both a per protocol basis (Figure 3) and on an intention to treat basis (mean PBC-40 Cognitive domain pre-treatment 20.9 ± 4.7 (possible value range 6-30) v post-treatment 18.2 ± 5.3;
p<0.0005) (Table 2). No significant improvement was seen in other PBC-40 domain scores following Modafinil therapy following correction for multiple testing.
Discussion

Recent studies have suggested that sleep disturbance is a significant problem in PBC, with patients being particularly troubled by excessive daytime somnolence (2,10). Modafinil is already widely, and effectively, used in the treatment of daytime somnolence in a number of disease settings including in narcolepsy. The first observation from this open label study is that Modafinil also appears, within the constraints of a study of this type, to be effective in the treatment of daytime somnolence in the PBC. The majority of patients who were able to tolerate the drug showed reduction in daytime somnolence. The degree of improvement seen in ESS was equivalent to that deemed to be clinically significant in other disease settings such as obstructive sleep apnea and narcolepsy.

Previous studies have demonstrated that, in addition to being an important factor in QOL impairment in its own right, daytime somnolence in PBC is strongly associated with the presence of the often life-altering fatigue that characterises this condition (10). Weaker associations are also seen with the other symptoms of the disease, including those associated with cognitive impairment. Given the strength of the association between daytime somnolence and fatigue in PBC we were interested in the extent to which Modafinil might also modulate other characteristic symptoms of PBC. We therefore examined the effects that modafinil had on the symptoms of PBC, including fatigue, assessed using the domain-based, disease-specific quality of life measure the PBC-40 (18). In keeping with our previous observations (10), the presence of excessive daytime somnolence in the current study cohort was again found, on pre-treatment assessment, to be associated with the presence of significant fatigue (10). Modafinil treatment was associated with improvement in PBC-40 fatigue domain scores in 86% of the series members who were able to tolerate it (57% of the whole cohort). The change in PBC-40 fatigue domain scores (ranging from 18-94%) was markedly greater than the relatively low degree of natural variation in PBC-40 fatigue domain scores identified on repeat testing during the psychometric evaluation of the PBC-40 (18). The apparent effects of modafinil on fatigue in PBC patients identified in this case series extend the important earlier observations made by Kaplan & Bonis by increasing the numbers of patients treated, by quantifying the effect on fatigue, and by demonstrating a clear link with the effect of modafinil on daytime somnolence (15). The beneficial effect of modafinil on fatigue in PBC mirrors
that seen in other disease states including narcolepsy (20), HIV infection (21), depression (22) and multiple sclerosis (23,24).

At present it is unclear whether any improvement in fatigue seen with modafinil is a specific or a non-specific effect. This reflects our current lack of understanding of the mechanisms whereby cholestasis, daytime somnolence, and fatigue are inter-related. Further studies are required in this area. Studies on the mechanisms of action of modafinil have focused, in general, on direct CNS effects (25,26). Such a direct stimulatory effect is clearly a plausible mechanism for the effects on both sleep disturbance and fatigue in PBC. A potential alternative mechanism for the effects of modafinil on fatigue in PBC would, however, be via its effects on the autonomic nervous system and blood pressure regulation (26,27). Autonomic dysfunction, including hypotension and impaired blood pressure regulation, is a common feature in PBC patients and one which appears to associate with fatigue severity (28,29).

In addition to the significant effect of modafinil therapy on fatigue a more modest improvement was seen with regard to symptoms of cognitive dysfunction in the modafinil treated PBC patients. This link between improvement in fatigue severity, improvement in severity of cognitive symptoms and reduction in daytime somnolence is in keeping with our earlier observation that PBC-40 Cognitive domain scores are associated with both PBC-40 Fatigue domain scores and ESS scores suggesting the presence of a linked aetiological process (10,19). It is interesting to note, in light of the apparent effects of modafinil on cognitive symptoms in PBC, that this agent was previously been demonstrated to objectively improve cognitive function in other sleep disturbance settings (30). Although slight improvement in other PBC-40 domain scores was seen with modafinil therapy none of the changes were statistically significant following correction for multiple testing.

Although this study has identified improvements in both daytime somnolence and fatigue in PBC following treatment with modafinil, and highlights the potential that this agent holds for the treatment of these difficult to manage symptoms of the disease, there are important outstanding aspects of the response which need to be addressed. Firstly, and most importantly, these observations clearly need to be confirmed in a placebo-controlled trial. Previous experience of therapeutic agents offering promise for the treatment of fatigue in PBC has shown discrepancy between open label and subsequent placebo-controlled studies. A key issue will be the nature of
the design of the definitive placebo-controlled trial. Recent observations have suggested that the
previously-used crossover protocol may not be appropriate for use in the PBC fatigue setting (31).
A second important question will be the sustainability of any response to modafinil both in terms of
daytime somnolence and of fatigue. Whereas no suggestion of tachyphalaxis was seen in this
study the maximum length of time for which patients received the agent was only 2 months. Given
that fatigue appears to be a highly stable and none naturally resolving symptom in PBC the
implication is that long term treatment will be necessary (32). Appropriate consideration should be
given to the pattern of dosing appropriate to give a long term sustained response. A major
limitation of many previous studies of symptom-directed therapy in PBC (particularly relating to the
other characteristic symptom of itch) is that they have looked only at short term response to
treatment and have failed to address the need for long term treatment with sustained safe function.

In conclusion, this open label study would appear to support the previous observation that
daytime somnolence is a significant factor in the expression of fatigue in PBC, and adds weight to
early reports suggesting that modafinil reduces fatigue in PBC by replicating, extending and
objectifying the findings. A placebo controlled trial in now warranted to confirm the effectiveness of
this agent and to determine the extent to which side-effects, exemplified by headache may, as in
other disease settings (33,34), limit its usefulness.
References


## Tables

**Table 1:** Clinical details of the series of patients receiving Modafinil

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>56 [38-72]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex (%)</td>
<td>100</td>
</tr>
<tr>
<td>Median [range] UDCA dose (mg)</td>
<td>600 [0-1200]</td>
</tr>
<tr>
<td>Disease stage at last biopsy</td>
<td>7/1/13</td>
</tr>
<tr>
<td>(Number of subjects with each stage early/advanced/No biopsy)</td>
<td></td>
</tr>
<tr>
<td>Bilirubin (µmol/l) median [range]</td>
<td>9 [5-19]</td>
</tr>
<tr>
<td>Albumin (g/l) median [range]</td>
<td>40 [34-50]</td>
</tr>
<tr>
<td>Alkaline phosphatase (IU/l) median [range]</td>
<td>110 [90-240]</td>
</tr>
</tbody>
</table>

**Table 2:** Percentage improvement in PBC-40 domain scores seen with Modafanil therapy. Improvements that are statistically significant following correction for multiple testing are denoted in bold

<table>
<thead>
<tr>
<th>PBC-40 Domain</th>
<th>Mean % Improvement (Intention to Treat Analysis)</th>
<th>Mean % Improvement (Per-Protocol Analysis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>58</td>
<td>87</td>
</tr>
<tr>
<td>Cognitive</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>Itch</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>Social &amp; Emotional</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Other Symptoms</td>
<td>8</td>
<td>12</td>
</tr>
</tbody>
</table>
Figure 1: Daytime somnolence in PBC patients prior to (pre), and 2 months after the institution of Modafinil (post) in patients able to tolerate Modafinil therapy.
Figure 2: PBC-40 Fatigue domain scores prior to (pre) and at 2 months following the institution of Modafinil (post) in patients able to tolerate Modafinil therapy
**Figure 3:** PBC-40 Cognitive domain scores prior to (pre) and at 2 months following the institution of Modafinil (post) in patients able to tolerate Modafinil therapy.