Exceptional surveillance review 2016 – Alcohol-use disorders (2010) NICE guideline CG100

Appendix A: summary of new evidence

Alcohol-related liver disease – corticosteroid treatment for alcohol-related hepatitis

100 – 01	**In patients with acute alcohol-related hepatitis, what is the safety and efficacy of corticosteroids versus placebo? / What is the safety and efficacy of corticosteroids for acute alcohol-related hepatitis?**

Recommendations derived from this question

1.3.3.1 Offer corticosteroid treatment to people with severe acute alcohol-related hepatitis and a discriminant function of 32 or more.

Surveillance decision

This review question should be updated.

2-year Evidence Update (2012)
An RCT and a Cochrane review evaluating pentoxifylline for alcoholic hepatitis were included in the Evidence Update.

A 3 month RCT compared pentoxifylline with prednisolone in people with severe alcoholic hepatitis (n=74) and found that mortality was higher with prednisolone[1].

A Cochrane[2] review of pentoxifylline found that it reduced mortality compared with control. However, the majority of the included trials showed a high risk of bias, and trial sequential analysis (which adjusts for multiple testing on accumulating data) did not support this result. The authors concluded that the evidence was not strong enough to determine whether pentoxifylline has a positive, negative, or neutral effect in alcoholic hepatitis.

Overall, the Evidence Update concluded that the identified evidence was limited and unlikely to impact on the guideline recommendation. The STOPAH trial was noted as being underway when the Evidence Update was developed and it was felt that it would be pertinent to await the results of this trial before considering any impact on the guideline.

4-year surveillance summary (2015)
A systematic review and 4 RCTs were identified at the 4-year surveillance review.

One RCT evaluated the addition of pentoxifylline to prednisolone for 28 days compared to prednisolone alone in patients who were heavy drinkers with severe biopsy-proven alcoholic hepatitis (n=270)[3]. This study found that response to therapy was not different between the two groups at 7 days. Furthermore, the addition of pentoxifylline did not alter 6-month survival.

A second study that evaluated combined pentoxifylline and prednisolone versus pentoxifylline alone in people with acute alcoholic hepatitis (n=62) found that there was no additional benefit with combination therapy compared to monotherapy on mortality and morbidity at 1 year[4].

In addition, a systematic review (which included 10 trials, n=884) indicated that pentoxifylline was more effective than placebo for the prevention of hepatorenal syndrome but provides no survival benefit at 1 month in people with severe alcoholic hepatitis[5]. Furthermore, trials of pentoxifylline versus corticosteroid, or as combination therapy did

not indicate any difference in reported outcomes.

An RCT evaluated the impact of the 30 day addition of metadoxine (unlicensed for this indication), to standard treatment with glucocorticoids (prednisone) in patients with severe alcoholic hepatitis (n=70) compared to prednisone[6]. Metadoxine adjunctive treatment increased 30 and 90 day survival and reduced the development or progression of encephalopathy and hepatorenal syndrome with the response to treatment being higher in those treated with metadoxine.

Finally, an RCT which compared combination therapy with glucocorticoids plus N-acetylcysteine with glucocorticoids alone in patients with severe alcoholic hepatitis (n=174) found that the addition of N-acetylcysteine did not alter 6 month survival[7].

Clinical feedback from the surveillance highlighted that the STOPAH trial was underway: a large UK RCT of prednisolone or pentoxifylline alone or in combination compared to placebo in people with alcoholic hepatitis. It was noted that this trial was due to publish in early 2015.

Overall, the 4-year surveillance review concluded that there was no impact on guideline recommendations. NICE CG100 recommends corticosteroid treatment for severe acute alcoholic hepatitis. The new evidence on the use of pentoxifylline alone or in combination with prednisolone was considered to provide a limited and heterogeneous evidence base. As forthcoming results were expected from the STOPAH trial, it was decided to wait for this trial to publish before assessing any need to update this section of the guideline.

Exceptional surveillance review (2016)
Stakeholders made us aware of publication of the STOPAH trial results and it was considered pertinent to review the data and assess any impact on the guideline recommendations. A focused search for the review question was conducted to identify any additional studies that had published since the last surveillance review. Overall, 4 studies were included.

Two outputs of the STOPAH trial were identified; both an RCT and a full HTA report[8,9]. As described above, the trial evaluated the effect of treatment with prednisolone or pentoxifylline in patients with alcoholic hepatitis and severe disease. Patients were allocated to one of four groups:

- Pentoxifylline-matched placebo and a prednisolone-matched placebo
- Prednisolone and a pentoxifylline-matched placebo
- Pentoxifylline and a prednisolone-matched placebo
- Prednisolone and pentoxifylline

The primary end point was mortality at 28 days. Secondary end points included death or liver transplantation at 90 days and at 1 year. Overall survival (OS) was also evaluated, for which an event was defined as any death occurring during 1-year post-treatment. A health economic evaluation was also conducted as part of the study.

The results indicated that pentoxifylline did not improve survival in patients with alcoholic hepatitis. Furthermore, prednisolone was associated with a reduction in 28-day mortality that did not reach significance but was associated with significantly more serious infections. At 90 days and 1 year there were no significant differences in mortality rates between the treatment groups.

The economic evaluation reported in the HTA aimed to determine which single treatment (pentoxifylline or prednisolone), dual treatment (pentoxifylline and prednisolone) or standard care (placebo) was the most cost-effective option when treating alcoholic hepatitis. A model was built to estimate the cost-effectiveness of the treatment arms over a 1-year period and over a patient's lifetime. The authors noted that because of decisions made about the choice of parameter values used in the model, the model-based evaluation is highly conservative against the prednisolone alone treatment strategy. Overall, the results of the within-trial analysis suggested that prednisolone might be considered cost-effective compared with the other treatment options. This result was considered to be supported by a deterministic model-based cost–utility analysis with a 1-year time horizon. Despite this result, the HTA concluded that there is considerable uncertainty remaining over long-term cost-effectiveness of treatment options and conclusions about the use of

prednisolone alone in the longer term remain inconclusive.

A multicentre randomised non-inferiority trial assigned 121 patients with severe alcoholic hepatitis to receive either pentoxifylline (400 mg, 3 times daily) or prednisolone (40 mg daily)[10]. At 7 days, the response to therapy was significantly lower in the prednisolone group than in the pentoxifylline group. There was a significant difference in 1-month survival rate of patients receiving pentoxifylline compared with prednisolone. However, there was no significant difference in 6-month survival rate between the two groups. Adverse effects were similar in both groups.

Finally, a systematic review and network meta-analysis (NMA) assessed the comparative effectiveness of pharmacological interventions (corticosteroids, pentoxifylline, and N-acetylcysteine [NAC], alone or in combination) for severe alcoholic hepatitis[11]. The results of a meta-analysis indicated that only corticosteroids decreased the risk of short-term mortality. The results of the NMA supported the use of corticosteroids alone or in combination with pentoxifylline or NAC to reduce short-term mortality. No treatment was effective in reducing medium-term mortality.

Topic expert feedback
Feedback from topic experts indicated that the current recommendation on corticosteroids for acute alcohol-related hepatitis should be revisited in light of the data from the STOPAH trial.

However, it was highlighted that not everyone participating in the STOPAH trial had a biopsy to confirm they had alcoholic hepatitis which may have impacted on the results of the study.

Furthermore, topic experts notified us to indicate that two Cochrane reviews in this area are being updated and expected to publish early 2016:

- Whitfield et al. Pentoxifylline for alcoholic hepatitis. Cochrane Database of Systematic Reviews 2009.
- Saconato H, Gluud C, Christensen E, Atallah ÁN. Glucocorticosteroids for alcoholic hepatitis (Protocol). Cochrane Database of Systematic Reviews 1999

Impact on guideline
Overall, the results of the STOPAH trial suggest that neither prednisolone (a corticosteroid) nor pentoxifylline were found to influence mortality or the need for liver transplantation at 90 days or 1 year in people with alcoholic hepatitis. Similarly, the evidence identified from the 2015 4-year surveillance review, also broadly indicated that pentoxifylline or prednisolone did not alter survival in people with severe alcoholic hepatitis.

This new evidence appears contradictory to the evidence included in the guideline as steroids were associated with a significant reduction in both all-cause mortality at one month and six months and liver-related mortality follow-up at one month in people with severe hepatitis. There were no significant differences between steroids and control for liver-related mortality follow-up six months. At the time of development, the Guideline Committee were aware of the ongoing STOPAH trial and had the view that the results of the trial would further inform the best treatment approach for these patients.

The new evidence available from the recently published STOPAH trial in addition to the studies identified through the recent surveillance review suggest that recommendation 1.3.3.1, which states that people with severe acute alcohol-related hepatitis and a discriminant function of 32 or more should be offered corticosteroid treatment, may no longer be justified.

New evidence identified that may change current recommendations.

References

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