Advice for managing patients with PBC unresponsive to UDCA

NHS England has written recently to the Medical Directors of a number of Hepatology services regarding the use of Obeticholic acid in patients with PBC.

NICE in its Technology Appraisal (TA 443) published 26th April 2017 has stated that:

> *Obeticholic acid is recommended, within its marketing authorisation, as an option for treating primary biliary cholangitis in combination with ursodeoxycholic acid for people whose disease has responded inadequately to ursodeoxycholic acid or as monotherapy for people who cannot tolerate ursodeoxycholic acid. Obeticholic acid is recommended only if the company (Intercept) provides the discount agreed in the patient access scheme.*
>
> *Assess the response to obeticholic acid after 12 months. Only continue if there is evidence of clinical benefit.*

NHS England will commission obeticholic acid according to the criteria contained within this guidance from 25th July 2017 within specialised hepatobiliary centres that meet the stated criteria, which has been informed by advice from the National Clinical Reference Group for Hepato-pancreas-biliary disease.

It should be noted that obeticholic acid will only be funded for patients registered via the Blueteq system and where an appropriately constructed MDT has approved its use.

In addition:

- *Trusts must purchase obeticholic acid at the agreed PAS discount price.*
- *Trusts must ensure use of obeticholic acid is approved via an existing MDT structure (meeting at least monthly) and in a service with 24/7 hepatology support / 2 WTE hepatologists*
- *Trust must complete a Blueteq form for all new patients receiving obeticholic acid.*
- *Trusts should commit to submitting data to the UK PBC registry*

The UK-PBC network identified a failure to respond to Ursodeoxycholic acid in those with primary biliary cholangitis (PBC), measured as a fall in the Alkaline Phosphatase, as a means to stratify patients with a poor prognosis. Those responding to Ursodeoxycholic acid with a reduction in the alkaline phosphatase pursue a much more benign course.

Obeticholic acid has been licensed recently for patients with PBC unresponsive to Ursodeoxycholic acid and is now available in the UK based on recent published data from prospective randomised controlled clinical

trials. Treatment should be evaluated after one year to determine whether long-term therapy is justified.

It is noteworthy that the management of patients on Obeticholic acid is considered complex since dose reductions are required in those with cirrhosis and that one significant side effect is pruritus, already problematic in PBC, which may require dose modifications. For these reasons and the consideration that patients with PBC to be offered Obeticholic acid have a poor outcome by definition, it is recommended that such patients should be managed in level 2 centres to ensure adequate expertise. Given the small number of patients involved and the need to concentrate expertise in the use of these new drugs a small number of centres have been selected. Furthermore, it is expected that clinicians involved in managing these patients will collate data in this high-risk group through UK-PBC to allow national evaluation of efficacy outwith the context of clinical trials. Long term data on liver failure and survival with Obeticholic acid have not been reported and the licensing decision was based on a surrogate marker i.e. the biochemical response measured as the change in alkaline phosphatase with Ursodeoxycholic acid.

An alternative to Obeticholic acid is to consider Bezafibrate or Fenofibrate. Neither is licensed for patients with PBC as disease modifying drugs, although patients may have received these agents as part of managing associated hyperlipidaemia. Meta-analyses of Fenofibrate or Bezafibrate in patients with PBC unresponsive to Ursodeoxycholic acid and a recent European prospective randomised controlled clinical trial in a similar population comparing Bezafibrate with placebo all demonstrated improved liver biochemistry. By virtue of their availability over many years toxicity, interactions (especially with statins) and side effects with Fibrates are well described. No positive effect on liver failure or mortality in PBC has yet been reported. Again, by virtue of the population under consideration for therapy it is recommended that patients should be managed in level 2 centres with data collection through UK-PBC considered desirable. If clinicians do wish to prescribe unlicensed drugs then, as always, this should be discussed with the patient and the discussion noted in the medical records.

Further reading

NICE:

https://www.nice.org.uk/guidance/ta443

EASL recommendations:

http://dx.doi.org/10.1016/j.jhep.2017.03.022

BSG recommendations:

Presented as a poster at BSG 2017 in Manchester, June 2017. *Paper in press*.

Papers published:

Hirschfield G et al. Efficacy of Obeticholic Acid in Patients With Primary Biliary Cirrhosis and Inadequate Response to Ursodeoxycholic Acid. Gastroenterology 2015; 148: 751 – 761.

Nevens F et al. A Placebo-Controlled Trial of Obeticholic Acid in Primary Biliary Cholangitis. N Engl J Med 2016; 375: 631 – 643.

Grigorian AY et al. Fenofibrate is effective adjunctive therapy in the treatment of primary biliary cirrhosis: A meta-analysis. Clin Res Hepatol Gastroenterol. 2015; 39: 296 - 306.

Zhang Y et al. Combination therapy of fenofibrate and ursodeoxycholic acid in patients with primary biliary cirrhosis who respond incompletely to UDCA monotherapy: a meta-analysis. Drug Des Devel Ther. 2015; 9: 2757 - 66.

Yin Q et al. Systematic review and meta-analysis: bezafibrate in patients with primary biliary cirrhosis. Drug Des Devel Ther. 2015; 9: 5407-19.

Corpechot et al. A 2-year randomised, multicentre double-blind placebo controlled study of Bezafibrate for the treatment of primary biliary cholangitis in patients with inadequate biochemical response to ursodeoxycholic acid. Presented at ILC, 2017. ILC abstract LBO81.