NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Rifaximin for maintaining remission from episodes of hepatic encephalopathy

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Dr Debbie L Shawcross

Name of your organisation: King's College London and King's College Hospital NHS Foundation Trust

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? ☑
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? ☑
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? ☑
- other? (please specify)
- I am an academic hepatologist and clinician scientist with a specific research interest in hepatic encephalopathy. ☑

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What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Cirrhosis of the liver is now the 5th commonest cause of death in the UK. It kills 15,200 people each year. Strikingly, it kills people on average 19 years younger than cancer or heart disease. The complications of cirrhosis include variceal bleeding, ascites, bacterial peritonitis, susceptibility to infection and hepatocellular carcinoma. Perhaps, one of the most neglected complications however is hepatic encephalopathy (HE) which can affect up to 80% of all patients with cirrhosis. Most commonly patients develop minimal or subclinical HE which has devastating impact on the quality of life of both patients and care givers. It causes short term memory loss, reversal of the sleep wake cycle, reduced reaction time, difficulty in concentrating, psychomotor dysfunction and sensory abnormalities. This impairs the ability of a patient for example to drive a car or take up employment.

Approximately 25-40% of these patients will go on to develop an episode of overt hepatic encephalopathy which is life-threatening and usually precipitated by a mild infection, dehydration or constipation. A large proportion of these patients will become comatose (grade 3 or 4 HE) which necessitates airway support, ventilation and admission to an intensive care unit. In a recent study published by my research group, only 52% of this cohort survived their intensive care stay and only 38% survived to hospital discharge, with 15% going on to be transplanted. *[Shawcross et al. Infection and systemic inflammation, not ammonia are associated with grade 3/4 HE but not mortality in cirrhosis. Journal of Hepatology 2011; 54:640-9]* These hospital stays are extremely expensive with immense NHS resource utilisation. The median cost of an ICU survivor in another recent study of mine was £51,376. *[Shawcross et al. The impact of organ failure in cirrhosis: survival at a cost? Journal of Hepatology 2012;56(5):1054-62]*

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Awareness of HE is very poor amongst primary care physicians and it often goes undiagnosed or may be misdiagnosed as dementia or Parkinson's Disease. Indeed, 25% of patients with HE can develop extra-pyramidal symptoms which mimic Parkinson's disease and do not respond to standard therapies. Some of these patients may be referred to neurologists and never get to see the appropriate clinician if cirrhosis remains undiagnosed. The vast majority of patients are managed within the hospital setting, usually after presenting for the first time with an episode of overt HE. There is wide variability in how the condition is managed within secondary care and only a select lucky few are referred to tertiary liver centres where they may be considered for liver transplantation or are reviewed by hepatologists with expertise in HE.

There is no drug currently licensed for the indication of HE in the UK. Lactulose (or lactilol) was used in the late 1970's and is the current mainstay therapy for the treatment of HE. The use of lactulose is based on the hypothesis that the colon is the primary organ responsible for generating ammonia. Lactulose is a laxative which lowers colonic pH through the production of organic acids by bacterial fermentation, thus creating an environment which is hostile to the growth of urease-producing gut flora, and conducive to the growth of non-urease producing species such as lactobacilli. The overall effect is to reduce production of ammonia in the colon. The acidification of colonic secretions also reduces absorption. Lactulose improves quality of life and cognitive function in patients with minimal HE, however a systematic review has not demonstrated a mortality benefit in patients with cirrhosis presenting with overt HE. At the same time as lactulose was introduced, the non-absorbable antibiotic neomycin was introduced but unfortunately ototoxicity and nephrotoxicity has rendered this treatment largely obsolete. Other antibiotics such as metronidazole were also utilised but this led to peripheral neuropathy. **It is therefore inappropriate to use neomycin as a comparator in the appraisal of rifaximin.**

In the main, lactulose or other laxatives are used in the outpatient setting in patients with minimal HE and to prevent those previously presenting with overt HE relapsing. However, this medication induces diarrhoea and bloating and is poorly tolerated by patients. When patients are admitted with overt episodes of HE, they are usually treated with enemas (if constipated) and any precipitating factors e.g. infection are treated.

Rifaximin-α is a non-absorbable antibiotic which has no known toxicities (although long term safety data have yet to be accumulated) which offers an alternative for this difficult to treat group of patients. It does not increase bowel frequency or bloating and has minimal systemic absorption (0.04%). A large double-blinded randomised controlled trial of 299 patients, conducted by Bass et al (NEJM 2010) demonstrated an improvement in maintained remission from HE and a reduction in hospitalisations due to HE over a six month period in patients with cirrhosis who were administered rifaximin versus placebo. Rifaximin has also been examined in the context of patients with minimal HE, examining its effect on driving performance over an eight-week period. Bajaj et al illustrated that the group randomised to rifaximin had significantly improved driving simulator performances compared to the placebo group. Increased levels of the anti-inflammatory cytokine IL-10 were found in the rifaximin-treated group which may allude to its mechanism of action being an anti-inflammatory rather than ammonia-lowering in nature. Indeed, rifaximin has not been shown (to my knowledge) to lower blood ammonia in any study to date and may rather than

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decreasing gut ammonia production, alter the make-up of the gut microbiome resulting in reduced bacterial translocation and endotoxemia which is prevalent in those with advanced cirrhosis. This lowers inflammation within the bloodstream which has been shown to be a major driver in the pathogenesis of HE. In fact, patients may have normal blood ammonia levels but still develop HE due to the presence of systemic inflammation.

There are no clinical guidelines that exist for the treatment of HE in the UK, Europe or USA although European guidelines (EASL) are currently being drafted following the licensing and approval of rifaximin in Europe and the USA after it received FDA approval in March 2010. These guidelines are likely to recommend rifaximin in combination with lactulose for the secondary prevention of HE in patients who have been previously hospitalised.

Rifaximin-α is being used on a named patient basis in selected liver centres in the UK by hepatologists with an interest in the treatment of HE. However, the failure to recoup costs from PCTs/commissioning groups has resulted in only a select few patients being treated. I have a specialist HE clinic at King's and am one such centre. I have now personally treated with rifaximin over 100 patients with minimal and recurrent overt HE leading to multiple hospital admissions that have been referred from all over the UK. From a personal standpoint, I have found the drug to be extremely efficacious. In many cases patients who had been requiring 5-6 hospital admissions over a 6 month period were treated successfully keeping them out of hospital and reducing the burden on carers. Specifically, I have found the drug useful in treating patients with large shunts e.g TIPSS and in those with the Parkinsonian phenotype of HE. Subjectively and objectively (measuring neurocognitive function pre- and post rifaximin), the drug has reduced disability and hospital admissions and improved quality of life. Other than nausea, I have not come across any significant side effects and there have been no cases of clostridium difficile diarrhoea which was a concern amongst clinicians. I have prescribed the drug in conjunction with lactulose (or other laxatives) but have also used it alone (in those intolerant of lactulose) with equally good results.

I think that it will be important for patients suspected of having HE to be reviewed by gastroenterologists and hepatologists in secondary care and for prescription of the drug to be recommended by experts in this setting. I would not advocate the blanket use within primary care as it is important to properly diagnose these patients and refer them for liver transplantation if indicated. I do not anticipate additional training costs or the need for additional specialist input.

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The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

I think that rifaximin can be used in the UK alone as well as in combination with lactulose although the main RCT (Bass study NEJM 2010) only examined its efficacy in combination with lactulose as ethical approval would not be granted to compare the drug against placebo. There is less rigid use of lactulose in the UK compared to the USA and therefore it may not be relevant for the drug to be licensed for use with lactulose.

I currently assess the objective response of a patient to rifaximin by performing a number connection test A and B (a simple 5 minute paper and pencil test) before and 4 weeks after commencing the medication. If there is no improvement subjectively or objectively, then I recommend discontinuation of the drug. I would advocate such an approach more widely throughout centres. There is no need to perform more expensive brain imaging or electrophysiology.

The main RCT only examined recurrent episodes of HE over a 6 month period. We do not yet know what the impact on HE, hospital admissions or the development of other complications of cirrhosis will be over a longer time period. From experience, it appears that maximal benefits are often accrued up to a year after commencing the drug. This may be because the gut flora changes slowly over a prolonged time period.

I think the most powerful statistic from the Bass RCT is the number needed to treat which will be highly relevant to the NHS. Four patients needed to be treated for 6 months to prevent 1 episode of HE and nine patients needed to be treated for 6

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months to prevent 1 hospital admission. Bearing in mind how costly and often prolonged such admissions are this will offer a considerable cost saving to the NHS.

Side effects in my experience are trivial. Nausea has been the most common in my opinion. I have not personally seen any cases of bacterial resistance or clostridium difficlie diarrhoea which was a major theoretical concern by microbiolgists.

I would not recommend the use of rifaximin in patients who are active alcohol drinkers or who are taking other antibiotics concurrently as these will override any favourable impact rifaximin has on gut flora.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

I am currently coordinating a national UK audit of rifaximin outcomes including impact on hospital admission rates in HE by secondary and tertiary liver centres which includes the data from our own practice at King's. These data are still being complied and are not currently available but may be available for review at the time of the NICE Appraisal.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

I do not think introduction of this therapy will impact on delivery of care or necessitate additional education and training. This drug is already being used for the treatment of traveller's diarrhoea throughout the UK and thus is already widely available.

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