Herefordshire and Worcestershire Medicines and Prescribing Committee

NHS
Herefordshire and Worcestershire
Clinical Commissioning Group

Guidelines for the Initiation and On-going Treatment of Rifaximin for Preventing Episodes of Overt Hepatic Encephalopathy

Recommendations: Shared care is suitable for on-going treatment of rifaximin for preventing episodes of overt hepatic encephalopathy

- General Prescribers (GPs) may be asked to prescribe on-going supplies for patients in whom rifaximin treatment has proven successful after at least a month's trial supplied via specialist teams.
- GPs will not be asked to initiate treatment with rifaximin.
- Responsibilities for monitoring are outlined for secondary and primary care below.

Indications for Rifaximin

Hepatic encephalopathy represents a reversible impairment of neuropsychiatric function associated with impaired hepatic function. Patients who have hepatic encephalopathy have clinically apparent impairments in cognitive and neuromuscular function. Overt hepatic encephalopathy (HE) affects 30-45% of patients with cirrhosis and minimal HE is seen in 20-80%. Survival after presenting with one episode of HE is 40% at one year and 20% at 3 years. The severity of overt HE is graded from I to IV based on clinical manifestations;

Grade I: Changes in behaviors, mild confusion, slurred speech, inversion of sleep/wake cycle
Grade II: Lethargy, moderate confusion
Grade III: Marked confusion, incoherent speech, sleeping but rousable
Grade IV: Coma, unresponsive to pain

There is a lack of understanding into this condition, but current therapies are based around either the ammonia or false neurotransmitter hypothesis. The ammonia hypothesis aims at reducing ammonia by decreasing ammonia substrates, inhibiting its production or increasing its removal. Treatment will vary according to the severity of the patient's HE. An elevated serum ammonia level in the absence of clinical signs of HE is not an indication for treatment. Treatment of HE includes determining the appropriate setting for care (an acute flare being managed in hospital) and excluding precipitating factors (eg variceal bleeding, electrolytes imbalance, dehydration, opiate medication, sepsis such as spontaneous bacterial peritonitis, constipation and such like).

Commonly used treatments for HE aim to reduce ammonia levels by decreasing production or absorption. This is accomplished by correcting hypokalaemia, giving lactulose and or antibiotics, favouring colonisation with non-urease producing bacteria. All patients with HE should be on regular lactulose (at a dose of up to 60mls in 2 or 3 divided doses) AND have evidence of validated breakthrough episodes of HE or refractory HE (eg EEG evidence or evidence encephalopathy in the presence of cirrhosis with portal hypertension). Those patients with suspect HE should be assessed by a Consultant Hepatologist or a Consultant Gastroenterologist with experience in treating liver disease, once other causes of encephalopathy have been excluded.

Rifaximin is a non-absorbable antibiotic which acts by inhibiting ammonia production. Rifaximin is licensed for the reduction in recurrence of episodes of overt Hepatic Encephalopathy (HE) in patients ≥ 18 years of age.[1] NICE has recommended rifaximin as an option for reducing the recurrence of episodes of overt HE in people aged 18 years or over.[2] In practice, rifaximin should be considered in all patients with persistent symptoms of encephalopathy despite lactulose or in lactulose intolerant patients or in those who have had 2 or more episodes of HE in the last 6 months.

Rifaximin is to be used in combination with lactulose which have been shown to reduce the symptoms of encephalopathy. A meta-analysis of rifaximin for HE found it had similar efficacy to lactulose for acute and chronic HE but was better tolerated. There is also evidence that rifaximin is effective in preventing recurrent episodes of HE in those with a history of recurrent admission with encephalopathy. When combined with lactulose there is complete resolution of HE in 75% of patients as opposed to 44% when treated with lactulose alone. There is also a reduction in mortality to 24% versus 50% when used in combination with lactulose versus lactulose alone.

The role of psychomotor testing and evaluation in the initiation of rifaximin for minimal-HE needs further investigation. Initiation of rifaximin cannot be recommended purely on the grounds of psychomotor impairment or behavioral change at present; consider enrolment in clinical trials.

The role of rifaximin for patients in whom the DVLA has previously withdrawn their driving license due to episodes of clinically overt HE has not been established. Clinicians are advised to refer patients whose symptoms resolve with regular rifaximin use back to the DVLA for advice.

Responsibilities of clinician initiating treatment – secondary care

1. Ensure patient is taking full dose lactulose (document where contraindicated or not tolerated)
2. Ensure the patient meets the criteria (see above) for treatment with **rifaximin (550mg twice a day)**
3. Discuss benefits and side effects of treatment with the patient and provide patient information leaflet (PIL) on rifaximin or see https://www.medicines.org.uk/emc/medicine/28104
4. Prescribe one month's supply of treatment. (The published data used rifaximin as a regular daily prescription, but intermittent supervised trials of therapy withdrawal to assess the need for continuation are to be encouraged as long as the patient will not come to harm)
5. Clinical assessment at one month, to include renal and liver function tests and full blood count.
6. If the patient is deriving benefits from rifaximin supply a further month's supply
7. Contact the patient's GP requesting on-going prescribing of rifaximin
8. Review the patient every 3 to 6 months to undertake routine clinical blood monitoring, review efficacy of and confirm the need for continuing treatment with rifaximin with the GP
9. Clinical benefit was established from a controlled study whereby subjects were treated for 6 months. Treatment beyond 6 months needs to take into consideration the individual balance of risk and benefit.

Responsibilities of clinician prescribing on-going rifaximin treatment – primary care

1. Agree to supply on-going prescribing of rifaximin
2. There are no specific monitoring requirements such as blood tests.
3. Prescribe rifaximin in response to consultant's feedback after each 3 to 6 month follow-up appointment

Responsibilities of the patient

1. Report to the doctor if there is not a clear understanding of the treatment and share any concerns in relation to treatment
2. Adhere to the treatment prescribed
3. Report any adverse effects whilst on treatment with rifaximin
4. Inform specialist or GP of any medication being taken, including over-the-counter products

Contraindications

- Documented drug allergy, rash and/or hypersensitivity to rifaximin, rifamycin-derivatives or to any of the excipients
- Pregnancy
- Prior non-response to therapy
- Intestinal obstruction

Cautions

- *Clostridium difficile* associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including rifaximin. The potential association of rifaximin treatment with CDAD and pseudomembranous colitis (PMC) cannot be ruled out.
- Due to the lack of data and the potential for severe disruption of gut flora with unknown consequences, concomitant administration of rifaximin with other rifamycins is not recommended.
- Patients should be informed that despite the negligible absorption of the drug (less than 1%), like all rifamycin derivatives, rifaximin may cause a reddish discolouration of the urine.
- The lack of safety data in Child-Pugh C cirrhosis (or MELD>25) means that the drug should be used with caution in advanced liver disease.
- Due to the effects on the gut flora, the effectiveness of oral oestrogenic contraceptives could decrease after rifaximin administration. However, such interactions have not been commonly reported. It is recommended to take additional contraceptive precautions, in particular if the oestrogen content of oral contraceptives is less than 50 micrograms.
- Fertility and lactation: It is unknown whether rifaximin or its metabolites are excreted in human milk. Therefore, a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from rifaximin therapy taking into account the benefit of breast feeding for the child and the benefit for the woman.

Adverse effects

The most common reported side effects in trials were psychiatric disorders, dizziness, headache, dyspnoea, abdominal pain and distension, nausea and vomiting, ascites, rashes, muscle spasm, arthralgia and peripheral oedema. Refer to the Summary of Product Characteristics for full details.

References:

1. Rifaximin Summary of Product Characteristics - http://www.medicines.org.uk/emc/medicine/27427
2. NICE Technology Appraisal guidance - TA337 (March 2015; reviewed June 2018): Rifaximin for preventing episodes of overt hepatic encephalopathy.
3. Vilstrup H *et al*. Hepatic encephalopathy in chronic liver disease; 2014 Practice guideline by the EASL and the AASLD J Hepatol 2014:61:642-659 https://www.journal-of-hepatology.eu/article/S0168-8278(14)00390-0/fulltext
4. Shawcross DL *et al.* How to diagnose and manage hepatic encephalopathy: a consensus statement on roles and responsibilities beyond the liver specialist. *Eur J Gastroenterol Hepatol* 2016;28:146-152 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4885589/

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