THE INTERNATIONAL LIVER CONGRESS (ILC) 2016: RIFAXIMIN USE IN CIRRHOSIS-RELATED HEPATOLOGICAL DISORDERS AND NEW PERSPECTIVES

Summary of the presentations on rifaximin from the Annual European Association for the Study of the Liver (EASL) meeting held in Barcelona, Spain, from 13th–17th April 2016

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ABSTRACT

Rifaximin (RFX)-α is a broad-spectrum antibiotic that targets commensal gut bacteria and reduces the excess ammonia produced by the gut bacteria of patients with cirrhosis. This innovative agent has been approved in most European countries for several therapeutic indications, including the prevention of episodes of overt hepatic encephalopathy (HE) in adult patients. New data on RFX use in HE were presented at the International Liver Congress (ILC), namely the annual meeting of the European Association for the Study of the Liver (EASL) held in Barcelona, Spain, from 13th–17th April 2016.

The beneficial effects of RFX have been attributed to the antibiotic action against a broad spectrum of gut bacteria, accompanied by the advantage of its very poor systemic absorption generating a gastrointestinal tropism. More recently, data are accumulating to suggest that other non-antibacterial effects contribute to RFX efficacy, making it a very interesting option for enteric diseases. RFX is thus explored outside of HE, in both cirrhotic and non-cirrhotic patients.

This review aims to highlight the presentations from ILC 2016 focussing on RFX developments in clinical research.

Keywords: Rifaximin (RFX), bacterial flora, hepatic encephalopathy (HE), cirrhosis, ascites, steatosis, bacterial peritonitis, non-alcoholic fatty liver disease (NAFLD), gut microenvironment, gut microbiota, inflammation.

INTRODUCTION

Rifaximin (RFX)-α (registered names, Normix®, Alfa Normix®, Colidimin®, Flonorm®, Lormyx®, Refero®, Spiraxin®, Targaxan®, Tixteller®, Tixtar®, Xifaxan®, Xifaxanta®, and Zaxine®) is a broad-spectrum antibiotic that targets commensal gut bacteria, including Gram-negative and Gram-positive aerobes and anaerobes, and that reduces the excess ammonia produced by the gut bacteria of patients with cirrhosis.[1] This innovative agent has been approved in most European countries for several therapeutic indications, including the prevention of episodes of overt hepatic encephalopathy (HE) in adult patients. HE is a debilitating complication that occurs as the main presentation of liver failure in cirrhotic patients; about 30–45% of these patients develop severe HE, which can be life-threatening.[2-4] Indeed, HE manifests as neuropsychiatric symptoms including disorientation, confusion, inappropriate behaviour, and personality changes.[5]

The indication approval for RFX use in HE followed pivotal clinical trial data demonstrating its efficacy

and safety.[6,7] New data on RFX use in HE was presented at the International Liver Congress (ILC), namely the annual meeting of the European Association for the Study of the Liver (EASL), held in Barcelona, Spain, from 13th–17th April, 2016. The beneficial effects of RFX have been attributed to the antibiotic action against a broad spectrum of gut bacteria, accompanied by the advantage of its very poor systemic absorption generating a gastrointestinal tropism. More recently, data are accumulating to suggest that other non-antibacterial effects contribute to RFX efficacy, making it a very interesting option for enteric diseases.[8] RFX is thus explored outside of HE, in both cirrhotic (cirrhosis has been linked to a pro-inflammatory milieu and hyperammonaemia) and non-cirrhotic patients.

This review aims to highlight the presentations from ILC 2016 focussing on RFX developments in clinical research.

NEW CLINICAL DATA ON HEPATIC ENCEPHALOPATHY

Efficacy and Safety of Rifaximin in Acute Hepatic Encephalopathy

Crisafulli et al.[9] initiated a randomised controlled trial to evaluate the impact of RFX dosage and combination with lactulose on HE stabilisation and resolution, in addition to the length of the patient's stay in the emergency department (ED). Seventy-seven patients were randomly assigned to either RFX 400 mg 4-times per day plus lactulose (Group A, n=39) or RFX 400 mg 3-times per day plus lactulose (Group B, n=38). Unsurprisingly, Group A patients experienced a faster HE reversion (3.35±1.16 versus 5.41±1.41 days, p<0.05), full disappearance of all symptoms (4.12±0.86 versus 6.33±0.59 days, p<0.05), and a shorter ED stay (5.7±3.8 versus 8.2±4.1 days, p<0.05).

In addition, this treatment arm showed a more significant decrease of ammonium between admission and 24 hours, versus Group B (35.23±8.56% versus 18.53±8.05%, p<0.005). When the baseline ammonium was >100 mg/dL, the difference between both treatment arms was even more significant (40.57±6.12% versus 20.74±6.56%, p<0.001). These results suggest that RFX plus lactulose, at both normal and high doses of RFX, is safe and effective as a first-line attack therapy in the context of the medical emergency that is acute HE.

Cost-Effectiveness of Rifaximin in the Prevention of Hepatic Encephalopathy Recurrence

HE generates a huge impact on patients' lives and represents a significant burden on healthcare systems.[2,10] At ILC 2016, new real-world clinical resource use data from the IMPRESS retrospective observational study were presented.[11] This study was conducted in 11 specialist National Health Service (NHS) centres in the UK, encompassing the medical records of 145 HE patients who had received RFX. Of note, 61% of patients were male, the mean age was 60.9±11.5 years, and 119 patients (82%) were on concomitant lactulose therapy. Child–Pugh score was recorded for 46% of patients, of which 10% were Class A, 54% Class B, and 36% Class C.

Resource use analyses were conducted in the 6 and 12 months pre and post-RFX initiation periods, only on patients who were alive at the end of each respective investigation period (6 and 12 months). At 6 months, RFX therapy was associated with significant reductions in hospital resources, namely mean hospital bed days per patient (28.6±3.1 versus 11.9±2.3, p<0.001), and hospitalisation frequency (2.2±0.2 versus 1.0±0.1, p<0.001) as compared with pre-RFX initiation. Total hospital bed days (n=101) were also reduced (mean 2,890 versus 1,206 days).

Similar findings were observed at 12 months, including significant reductions in mean hospital bed days per patient (31.7±3.6 versus 16.4±2.9, p<0.001) and hospitalisation frequency (2.7±0.3 versus 1.7±0.2, p=0.002), as compared with pre-RFX initiation. Total hospital bed days (n=99) were also reduced (mean 3,138 versus 1,621 days).

Of note, this study was the first to evaluate and demonstrate reductions in critical care bed days with RFX between the pre and post-initiation periods of 6 months (7.9 versus 2.0 days, p=0.046) and 12 months (11.3 versus 2.4 days, p=0.017). Significant reductions in hospital re-admissions and ED visits were observed, but only for the pre and post-initiation periods of 6 months.

Overall, RFX was well tolerated with only three patients (2%) reporting adverse events and four (3%) developing *Clostridium difficile* infection (none of these groups discontinued therapy). Interestingly, these findings are strongly aligned with those from another study conducted in seven liver centres across the UK that highlighted marked

reductions in the number of hospital admissions and hospital length of stay, demonstrating the cost-effectiveness of RFX for HE prophylaxis.[12]

RIFAXIMIN FOR SPONTANEOUS BACTERIAL PERITONITIS

Spontaneous bacterial peritonitis (SBP) is a serious and life-threatening liver cirrhosis complication with a high recurrence rate of 70% at 1 year.[13] Norfloxacin, a fluoroquinolone, is widely used for secondary prophylaxis to prevent recurrences of SBP in patients with liver cirrhosis and ascites. Due to the emergence of quinolone-resistant and Gram-positive SBP however, some specialists have suggested the use of RFX, which does not appear to promote the emergence of bacterial resistances.[13]

A randomised controlled trial of RFX versus norfloxacin in 262 cirrhotic patients with ascites and a previous episode of SBP[14] was conducted.[15] All patients were randomly assigned to receive either 1,200 mg RFX (n=103) or 400 mg norfloxacin (n=92), daily, for 6 months.

RFX was more effective than norfloxacin, since the recurrence rate of SBP was significantly lower in the RFX group (3.88% versus 14.13%, p=0.041) when compared with the norfloxacin group. Likewise, the mortality rate was significantly decreased in the RFX group (13.74% versus 24.43%, respectively; p=0.044). Regarding the safety profile of both regimens, RFX was associated with a lower rate of side effects versus norfloxacin (p=0.033), which makes intestinal decontamination with RFX a more attractive treatment option than norfloxacin based on the findings of this study.

RIFAXIMIN FOR NON-ALCOHOLIC FATTY LIVER DISEASE

Non-alcoholic fatty liver disease (NAFLD) may involve pro-inflammatory cytokines and increased insulin resistance, thus contributing to hepatic steatosis and BMI elevation. In an open-label, prospective, multicentre cohort study, the effect on NAFLD of a daily administration of 1,100 mg RFX for 6 months was evaluated in 126 NAFLD patients (42 steatosis and 84 non-alcoholic steatohepatitis [NASH]).[16]

The NASH group showed significant reductions in BMI, gamma glutamyl transferase (γ-GGT), alanine aminotransferase (ALT), endotoxin, pro-inflammatory cytokines (interleukin [IL]-6), tumour necrosis factor-α, IL-10, and cytokeratin-18 (CK-18). Similarly, patients with steatosis showed reductions in ALT, γ-GGT, and homeostasis model assessment score (a measure of insulin resistance). However, RFX therapy did not show a significant effect onserum levels of aspartate aminotransferase and lipid profile. Overall, RFX appeared to modify the pathogenesis of NASH through the reduction of serum endotoxin and improvement of insulin resistance, BMI, pro-inflammatory cytokines, and CK-18.

RIFAXIMIN FOR ASCITES

Refractory ascites (diuretic-resistant ascites and diuretic-intractable ascites) occurs in nearly 17% of cirrhotic patients.[17] An open-label, prospective, single-centre study aiming to evaluate standard diuretic therapy plus midodrine and RFX (800 mg RFX/day) against standard diuretic therapy in 400 cirrhotic patients (randomised at a ratio of 1:1 to either arm) with refractory or rapidly recurrent ascites was conducted.[18]

Adding RFX and midodrine led to a complete response in 78% of patients, partial response in 18%, and no response in 4% versus 15%, 55%, and 30% in the control group, respectively. By improving systemic and renal haemodynamics, as well as providing significant improvements on diuresis and weight loss, the combination therapy helped reduce paracentesis needs and control ascites. Midodrine and RFX also significantly improved short-term survival (12.6±3.2 months versus 6.6±2.2 months, p=0.000).

The authors concluded that adding RFX and midodrine to standard medical therapy is mandatory and advised to improve the systemic haemodynamics, the control of ascites, and short-term survival.

PRECLINICAL STUDY ON RIFAXIMIN AND SYSTEMIC/INTESTINAL INFLAMMATION

To assess the action of RFX on intestinal barrier, inflammatory milieu, and ammonia generation independent of the direct effect on microbiota, a preclinical study was conducted on germ-free 10-week-old GF C57/BL6 male mice; some of them were colonised with cirrhotic human stools, and RFX was administered to a subgroup of each group. RFX promoted intestinal homeostasis by

changing intestinal permeability and inflammatory markers, which could suggest a positive influence of RFX beyond antibiotic activity.[19] A beneficial impact was observed on serum ammonia through elevated small bowel tissue glutaminase, as well as a 3-fold increase in caecal glutamine content (p=0.02), even in the absence of microbiota. RFX positively altered the microbial functionality of the intestinal barrier without changing its composition, and beneficially impacted systemic and intestinal inflammation.

CONCLUSION

The evidence on the 'eubiotic' effects of RFX beyond its antibiotic properties, through changes in the metabolic function of the gut microbiota and microenvironment, continues to accumulate. New data presented at ILC 2016 further ascertained the clinical efficacy and safety profile of RFX in a range of hepatological and enteric disorders, including real-life data, which mirror the findings from pivotal clinical trials.

Although definitive studies on the effect of RFX on gut microbiota in larger cohorts of both healthy volunteers and patients are needed, the evidence for the use of RFX in several enteric diseases is becoming more robust, and supports the potential of this innovative compound to have a significant and positive impact on treatment outcomes and quality of life for patients.

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