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CORRESPONDENCE

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RE: Effects of Long-Term Norfloxacin Therapy in Patients With Advanced Cirrhosis

Dear Editors:

We have read with interest the work of Moreau et al,[1] a multicenter, double-blind, randomized trial evaluating the effects of long-term treatment with the fluoroquinolone norfloxacin on survival of patients with cirrhosis. Overall, therapy with norfloxacin did not reduce 6-month mortality. However, the authors reported a decrease in 6-month mortality in patients with ascitic fluid protein concentrations of <15 g/L and a decrease in the incidence of any and gram-negative bacterial infections.

The study addressed an extremely relevant topic, that in this era of growing concern about antimicrobial resistance has repercussions even outside the hepatological setting. Unfortunately, the study was performed on a smaller than planned sample, 291 patients, and, even more important, only patients who had not received fluoroquinolones within the past month were eligible to be included in the study.

In our opinion, excluding patients with recent exposure to fluoroquinolones significantly undermines the results of the study. Cirrhotic patients have a high probability of having been exposed to fluoroquinolones considering that, apart from being frequently used for the treatment of urinary tract infections and community-acquired pneumonia, they are recommended by both the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases as drugs of choice for treatment of spontaneous bacterial peritonitis.[2,3] The broad spectrum of activity of fluoroquinolones combined with the high frequency of mutations in the target bacterial enzymes led to a change in the microbiota of cirrhotic patients with a high prevalence of gram-positive bacteria and extended-spectrum β-lactamase-producing Enterobacteriaceae.[4] This is particularly relevant for the gastrointestinal tract, which is considered the reservoir of antibiotic resistance genes ("gut resistome").[5] Overall, excluding patients with recent exposure to fluoroquinolones creates a cohort who do not correctly mimic the real-world settings and, even if this is not the case, it could have led to a biased observation of norfloxacin efficacy in decreasing mortality.

Another important point is related to the growing concerns on fluoroquinolone safety profile. On November 16, the European Medicines Agency has released a review on quinolone and fluoroquinolone antibiotics recommending a restriction in these drugs use owing to the possible long-lasting, disabling, and potentially permanent side effects involving tendons, muscles, joints, and the nervous system.[6] Several Food and Drug Administration Drug Safety Communications preceded the European Medicines Agency alert. They highlighted the association between fluoroquinolone/quinolone use and significant decreases in blood sugar and certain mental health side effects (07-10-2018), side effects involving the tendons, muscles, joints, nerves, and central nervous system (05-12-2016), peripheral neuropathy (08-15-2013) and an increased risk of developing tendinitis and tendon rupture (Boxed Warning, 07-08-2008). The amount of evidence is so relevant that in 2016 Food and Drug Administration has coined the term fluoroquinolone-associated disability to describe the syndrome related to fluoroquinolone exposure.[7] Moreover, recently published works evidenced an increased incidence of aortic aneurysm or dissection in association with oral fluoroquinolone use.[8] These side effects are especially relevant to the elderly and those with impaired renal function, a group of subjects well-represented among cirrhotic patients. It can be easily inferred that the longer the time of exposure to fluoroquinolones, the greater the risk of developing side effects. The long-term prophylaxis of spontaneous bacterial peritonitis with norfloxacin proposed in this study, lasting 6 months, largely overtake the 6–8 weeks recommended for vertebral osteomyelitis, a clinical situation with indication to the longest fluoroquinolone exposure. Overall, serious safety concerns arise considering translation of this work into clinical practice. It would really be important to know the amount and quality of fluoroquinolone-related side effects reported by subjects enrolled in the study, considering the absence of data on the topic.

In conclusion, future research should focus on the development of specific antimicrobial stewardship programs for cirrhotic patients, aimed to reduce total antibiotics exposure and to the identify those patients who are really in need of antimicrobial drug treatment of cirrhosis-related infectious complications. Moreover, the use of fluoroquinolones must be carefully considered, taking into account both side effects and the broad antimicrobial spectrum and high efficacy. The growing evidence of side effects in the setting of fluoroquinolone use should not lead to forget the benefits of these powerful drugs, especially in the complex patients such those with cirrhosis.

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References

1. Moreau R, et al. Gastroenterology 2018;155:1816–1827.e9.
2. Runyon BA. Hepatology 2013;57:1651–1653.
3. Angeli P, et al. J Hepatol 2018;69:406–460.
4. Marciano S, et al. Eur J Gastroenterol Hepatol 2018;1.
5. Schaik W van. Philos Trans R Soc B Biol Sci 2015;370.
6. European Medicines Agency. 2018;44. Available from: EMA Press Release https://www.ema.europa.eu/en/news/disabling-potentially-permanent-side-effects-lead-suspension-restrictions-quinolone-fluoroquinolone.
7. FDA Drug Safety Communication 07-26-2016. 2016.
8. Pasternak B, et al. BMJ 2018;360:1–8.

Conflicts of interest
The authors disclose no conflicts.

Most current article

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Goodbye for Good: Stepping Away From Recurrence

Dear Editors:

We read with great interest the article written by Montano-Loza et al in the recent issue of *Gastroenterology*.[1] The authors evaluated risk factors associated with recurrence of primary biliary cholangitis (PBC) after liver transplantation using a large international cohort from 13 institutes (10,754 transplanted patients including 825 PBC patients). The data were granular and they investigated in detail preoperative and postoperative laboratory data, immunosuppression regimens, and biopsy results, which are not available from registry data alone. They found a younger age at the time of diagnosis and, after receiving a liver transplant, use of tacrolimus, and severe biochemical cholestasis within the first 6 months after liver transplant increase the risk of PBC recurrence. Also, this study is the first to demonstrate the association between disease recurrence and impaired graft survival in PBC patients. We wish to point out several questions from the article.

The patients included in this study received their diagnosis of PBC between 1983 and 2016. In their discussion, the authors referred to the possibility of an "era effect" of the selection of the immunosuppression regimen. We also believe that temporal changes in diagnosing PBC, improvement of the management before and after transplantation, and the development of transplant surgery will be factors that should be considered during this time range. We would like to know how the authors will make assessments about the "era effect" in more detail. As well, we would like to ask about the effects of center-related factors. There is a study that showed significant differences in graft survival rates between liver transplant centers.[2] In this study, there are 13 centers of various countries involved. Other than different follow-up times and liver biopsy protocols, which is mentioned in this article, we assume that there are also differences in the management of PBC, surgical outcomes, and use of cyclosporine by center. To date, there have been several reports regarding preventative influences of cyclosporine on PBC recurrence according to single-center experiences. If the favorable influences of cyclosporine on PBC recurrence would be seen regardless of center, we think their conclusion will be much strengthened.

Second, according to the guidelines of European Association for the Study of the Liver,[3] antimitochondrial antibodies (AMA) are a hallmark of a diagnosis of PBC. [3] There is a report that AMA status does not affect the response in PBC patients to treatment with liver transplantation.[4] In contrast, there is an article that suggests AMA-negative PBC patients have significantly worse prognosis compared with AMA-positive PBC patients.[5] These studies are single center, with a limited number of cases. Again, because this study includes multiple centers with a large number of patients, we would like to ask if there was a correlation between AMA status and PBC recurrence.

Last, in statistical analyses, simple Cox proportional hazards regression may not be appropriate for recurrence analysis because it ignores the competing event. For this article, the competing event, that is, death after transplant before PBC recurrence, hinders the recurrence of PBC. More detailed assessments of competing event will enhance this study.

In conclusion, preventing PBC recurrence is pivotal in improving graft and patient survival. As shown in this study, immunosuppression regimen can potentially change the risk of PBC recurrence. We raise some questions for the authors that may further extend their findings. More detailed future investigations, using national registry data, would be helpful to understand the role of immunosuppression regimens, although a prospective, randomized, controlled trial needs to be conducted before the results can be deemed conclusive.

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References

1. Montano-Loza AJ, et al. Gastroenterology 2019;156:96–107.
2. Joris J, et al. Transplant Int 2018;31:610–619.