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Letter to the Editor

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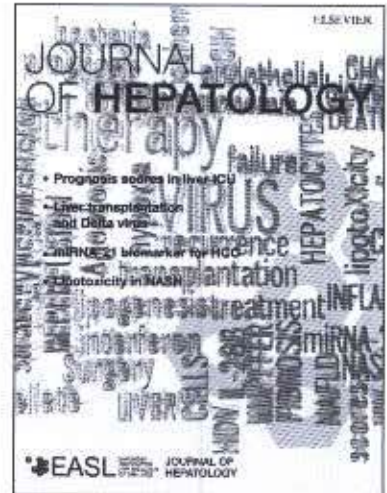
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Professor Rajiv Jalan
Editor, Journal of Hepatology

Dear Professor Jalan,

Reduced mortality due to phlebotomy in moderately iron-loaded HFE Haemochromatosis? The need for clinical trials

MB Delatycki^{1,2*}, LC Gurrin³, SY Ong¹, GA Ramm⁴, GJ Anderson⁴, JK Olynyk⁵, KJ Allen^{1,6}, AJ Nicoll⁷, LW Powell⁴

¹ Murdoch Childrens Research Institute, Parkville, Victoria, Australia

² Austin Health, Heidelberg, Victoria, Australia

³ Melbourne School of Population and Global Health, University of Melbourne, Parkville, Victoria, Australia

⁴ QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia

⁵ Fiona Stanley and Fremantle Hospitals, Western Australia; Curtin University, Western Australia; Murdoch University, Western Australia, Australia

⁶ Royal Children's Hospital, Parkville, Victoria, Australia

⁷ Eastern Health, Box Hill, Victoria, Australia

Corresponding Author- Professor Martin Delatycki E- martin.delatycki@ghsv.org.au, P- +61 3 9496 3027, F- +61 3 9496 4385

We read with interest the paper by Bardou-Jacquet and colleagues [1] examining mortality in HFE associated hemochromatosis and the accompanying editorial [2]. Both the authors of the study and the writers of the editorial concluded that the observation that HFE p.C282Y homozygotes with a serum ferritin (SF) at diagnosis between the upper limit of normal (ULN) and 1000µg/L have reduced mortality compared to the population at large is due to venesection therapy.

We are not convinced however, that this conclusion is supported by the data provided for the following reasons:

1. If normalization of SF resulted in reduced mortality then it would be expected that HFE p.C282Y homozygotes with normal SF at diagnosis would also have reduced mortality but this was not found to be the case.
2. There was no information about the amount of iron removed for 36% of subjects so there was likely to be a significant minority of individuals with SF between the ULN and 1000µg/L who did not have normalization of SF.
3. The cohort had a mean duration of follow-up of 8.3±3.9 years. The average age at diagnosis was 45.2±14.2 years. This means that it is likely that many subjects in the group with SF between the ULN and 1000µg/L had a raised SF for many more years than they had a normalized SF. It is not at all clear how this balance would result in reduced mortality when this was not seen among those with normal SF at diagnosis. Of those who did have information about the amount of iron removed, there is no information about whether they continued venesection therapy in order to maintain a SF level < 50µg/L after a SF of < 50µg/L was achieved initially, or the extent to which follow-up data (number and volume of phlebotomies, clinical and biochemical indicators of tolerance and efficacy of venesection therapy) were available. Moreover, there is no information about a formal, standardized, consistent, cohort-

wide protocol around advising participants to start, continue and potentially stop venesection therapy, which makes the claim that the results can be interpreted as "intention-to-treat" difficult to justify.

Reasons other than the benefit of normalization of SF that could explain the study findings include:

1. Having a mild excess of iron in the body reduces the risk of cardiovascular and extrahepatic cancer. This is counter intuitive with data suggesting that iron is pro-oxidant and therefore more likely to result in increased cancer incidence. In addition we found an increase in the incidence of breast and colorectal cancer in a large cohort of HFE p.C282Y homozygotes compared to a matched HFE wild-type control group, although we did not have sufficient data to examine the association of cancer occurrence with SF levels [3]. From the cardiovascular standpoint, there is evidence that low hepcidin levels that are associated with HFE p.C282Y homozygosity, leads to low reticuloendothelial cell iron levels despite high total body iron and that this can lead to reduced levels of atherosclerosis (the so called "hemochromatosis paradox") [4].
2. As noted by the authors, those with SF between the ULN and 1000 μ g/L had increased medical care compared to the average person and this may have resulted in other lifestyle changes that were beneficial. For example lifestyle changes in subjects with fatty liver disease such as diet and exercise, can improve liver function and morbidity. No information is given by the authors on body mass index and any changes in this following appropriate intervention.
3. Individuals with SF between ULN and 1000 μ g/L are less prone to iron deficiency anemia and this may result in health benefit.

The only way to answer the question of the role of venesection therapy in HFE p.C282Y homozygotes with SF between ULN and 1000 μ g/L is to do a randomized study with half the cohort having normalization of SF and the other half not being treated. Until such data are available, the question of benefit from treating HFE p.C282Y homozygotes with SF between ULN and 1000 μ g/L remains, in our view, unproven.

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