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Hepatology highlights

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Best J, *et al*. Mycophenolic acid induces apoptosis of hepatic stellate cells in an *in vitro* model of HCV

Best J, *et al*. The activated form of mycophenolate mofetil (MMF), mycophenolic acid (MPA), is a highly effective immunosuppressant that lacks the nephrotoxicity associated with calcineurin inhibitors that is often used to prevent rejection post-organ transplantation.[1] MPA inhibits inosine monophosphate dehydrogenase (IMPDH)[2] thus decreasing levels of intracellular guanosine nucleotide pools resulting in inadequate quantities for nominal DNA duplication. Hepatic stellate cells (HSC) are the key effectors in the development of liver fibrosis. The activation of previously quiescent HSC plays a pivotal role in fibrogenesis, potentially culminating in liver cirrhosis and organ dysfunction. On the other hand, immunosuppresion is mandatory after liver transplantation to avoid rejection processes. Hepatic macrophages promote the survival of activated HSC in a nuclear factor-kappaB- (NF-κB-) dependent manner and thereby promote liver fibrosis.[3] However, inhibition of NF-κB pathway reverses hepatic fibrosis by stimulating HSC apoptosis, thereby highlighting selective induction of HSC apoptosis as a promising strategy to treat liver fibrosis.[4] In this issue, Best, *et al*. have analyzed the effects of immunosuppressants in combination with hepatocyte apoptosis on HSC activation and viability. Their results show that mycophenolic acid had an overall strong effect on HSC apoptosis, viability and activation. Based on their in vitro model data, Best, *et al*. demonstrated that mycophenolic acid has potential to reduce renewed fibrosis in a post-transplant HCV infection. Due to some limitations due to the chosen model –*in vitro* cell cultures– more studies will be needed to assess the role of mycophenoloic acid in apoptosis.

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Adams PC, *et al*. Serum ferritin is a biomarker for liver mortality in the Hemochromatosis and Iron Overload Screening Study

Adams PC, *et al*. Hyperferritinemia is not just a marker of iron overload, but also of inflammatory processes, metabolic abnormalities and malignancies. The multivariate analysis in the current study demonstrated in a large cohort of Canadian patients that raised ferritin was related to shorter survival. Interestingly, some features related to iron overload like arthritis or sexual impotence were not related to survival but others like diabetes, liver disease and heart failure strongly influenced it. In spite of ferritin has been associated with non-alcoholic fatty liver disease (NAFLD), phlebotomies did not impact on transaminase levels, steatosis degree or cytokeratin-18 levels supporting the hypothesis of being more a marker of systemic inflammation than a

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related pathophysiologic event in this entity.[1] Interestingly, previous biomarkers like transaminases or C reactive protein have been found related to mortality in apparently healthy people.[2] Altered ALT level was related to decreased survival, mainly due to liver disease. CRP increased mortality associated to cardiovascular disease. Moreover, we need to add the relationship with malignancies to its role as acute-phase reactant. Thus, in clinical practice detection of high levels of ferritin in a non-HFE mutations setting should be keep in mind as a risk factor for impaired survival and diagnosis process should be implemented to detect inflammatory or neoplastic diseases that could underwent early treatment and improve prognosis.

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Persico M, *et al*.
HCV antiviral therapy in injection drug users: difficult to treat or easy to cure?

Persico M, *et al.* For Anglo-Saxon people, difficult-to-treat has been a synonymous of difficult-to-cure when talking about patients with hepatitis C and resistance to standard antiviral therapies. Interestingly, drugs users belong to an especial group of patients they are difficult-to-treat but easy-to-cure. Drug users are younger with less fibrosis and commonly infected by genotypes more sensitive to interferon (like genotype 3) and, thus achieved higher rates of sustained virological response (SVR), especially in patients achieving rapid virological response (negativity of HCVRNA at week 4 of therapy). Difficult-to-treat cases are patients with low adherence to therapeutic regimen due to drug addictions, psychiatric disorders or comorbidities. Improving compliance requires a multidisciplinary approach involving pharmacists, psychologists, nurses and hepatologists. Solà, *et al*. demonstrated that multidisciplinary approach improved not just adherence but also sustained virological response.[1] Thus, the key point is compliance to the therapy that in some circumstances could be very low, i.e. in active drug users; but in abstinent and recovered patients, compliance is common and SVR rate very high as demonstrated by Persico, *et al*. Current all-oral antiviral regimen seems to save safety concerns resulting in improved compliance. However, these drugs are more effective in genotype 1 and 4 than genotype 3 and for these patients easy-to-cure but difficult-to-treat new oral regimen remained elusive and further drugs are warranted.

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Faustini-Pereira JL, *et al*.
Exercise capacity of cirrhotic patients with hepatopulmonary syndrome

Faustini-Pereira JL, *et al.* This study focuses on the impact of physical exercise on hepato-pulmonary syndrome in cirrhotics. Regular and moderate exercise in patients in waiting list for orthotopic liver transplantation improved fitness, breathe strength, survival in waiting list and also post-transplant avoiding the negative effect of hepatopulmonary syndrome. Advanced liver disease influences on fitness and the ability to conduct daily activities and impairs quality of life. This manuscript highlights: First, physical activity prescription is overlooked in clinical practice and frequently just vague recommendations were transmitted to the patient. Besides, the impact of this exercise is commonly evaluated by quality of life questionnaires like SF-36 or CLDQ instead of maximun Volume of O_2 (maxVO_2). Second, submaximal exercise walking during 6 min could be routinely implemented because is a cheap and easy-to-do test to predict maxVO_2 consumed, a parameter strongly related to

survival in cirrhotics. Third, patients suffering from liver cirrhosis could tolerate physical exercise without negative impact on liver function. In summary, Faustini-Pereira, *et al*. recommended regular physical activity in cirrhotics to improve quality of life, metabolic derangement and decreasing risk for liver-related complications.

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