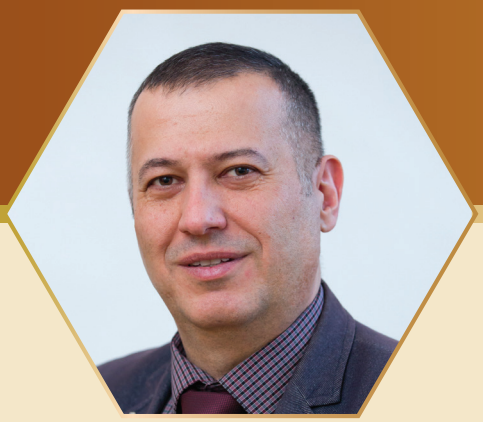
1st GLOBAL LIVER HEALTH FORUM

Importance of RWE in understanding the current disease landscape: MANPOWER results put into perspective



Prof Chavdar Pavlov

Head of the Department of Therapy and Head of the Center for Evidence Based Medicine,'Sechenov' First Moscow State Medical University, Russia.

Flash for webinar (~20 mins)

SANOFI

Importance of RWE in understanding the current disease landscape: MANPOWER results put into perspective

COVID-19 and liver disease

International registries have been set up to follow COVID-19 in people with pre-existing liver disease. From 25th March 2020 to 20th April 2020 (COVID-Hep.net and COVIDCirrhosis.org) registered 152 people from 21 countries), 95% of whom were hospitalised. The type of liver disease, cirrhosis or chronic liver disease was recorded as was its aetiology, viral, alcohol-related or NAFLD.[1]

According to data from large cohort of COVID-19 patients (N= 1 099), it was shown they have increased levels of AST and ALT in relation to the severity of their infection.[2]

Diagnostic tools for NAFLD

Ultrasound examination: a large-scale, prospective, cohort study, found that cardiovascular death risk was 2.8 times higher in patients with ultrasound-diagnosed steatosis over a 4-year follow-up period (3.6–4.8 years).[3]

When compared with histology, in terms of liver steatosis diagnostic specificity and sensitivity, ultrasound is an accurate and reliable method to detect steatosis (2–3 grade). A ROC = 0.93, confirms the high prognostic value of ultrasound in steatosis verification.[4]

Liver enzymes: increases in ALT and AST serve to alert clinical awareness of liver damage, but levels naturally fluctuate and may even normalize spontaneously. Measurement of ALT and AST levels does not reflect the extent of steatosis, fibrosis or even correlate with histological inflammation activity in NAFLD/NASH. Following untreated, NASH patients for 2 years found a natural ALT dynamic, levels constantly increased in 68% patients, spontaneously fluctuated up and down in 22% and spontaneously normalized in 10%.[5]

St-index: is a new non-invasive screening tool for suspected steatosis based on real world data. This simplified measure requires just a tape measure. The age of the patient their T2DM status and waist-to-height ratio are used in the following formula, Y= -3.5856 + 0.0141*age + 0.4711*T2D + 4.4373*WCHR.[6]

RWE: real-world evidence; **EPL:** essential phospholipids; **NAFLD:** non-alcoholic fatty liver disease; **NASH:** non-alcoholic steatohepatitis; **T2DM:** type 2 diabetes; **WCHR:** waist-to-height ratio; **RCT:** randomized controlled trial; **ROC:** receiver operating curve; **Alk Ph:** alkaline phosphatase; **GGT:** gamma-glutamyl transferase; **ALT:** alanine aminotransferase; **AST:** aspartate aminotransferase; **AEs:** adverse events.

Importance of RWE in understanding the current disease landscape: MANPOWER results put into perspective

Is intrahepatic cholestasis common in NAFLD?

A Russian study included 163 subjects with simple steatosis to cirrhosis to investigate the incidence of intrahepatic cholestasis (IHC) in NAFLD and found few signs of its presence, with on average, normal bilirubin levels and increased Alk Ph levels evidenced in 30% of patients.[7]

Evidence for essential phospholipid use in NAFLD

In an analysis of pharmacotherapy options used as adjunct treatment in NAFLD, only EPL had confirmed effectiveness on steatosis in NAFLD - 5 RCTs. A recently published meta-analysis of 10 RCTs confirms this finding.[8]

The clinical efficacy of EPL in steatosis has been demonstrated in data from China where reversal of steatosis in NAFLD + 2TDM, or its improvement to mild steatosis, was shown in 65% of the 85 patients treated with EPL (1.75 – fold higher than in controls, $p<0.05$ vs. control). This latter group was treated with metformin and all the participants received diet and physical activity recommendations.[9]

The mode of action of EPL is to correct for the decreased amount of phosphotidylcholine which might lead to the development of NAFLD and the progressive functional disorders in the liver.

This decrease of PPC level is characterized by:

- Excessive fatty acid and triglyceride synthesis
- Insufficient fatty acids oxidation (β-oxidation in mitochondria)
- Defective very low-density lipoproteins secretion and excretion.[10]

RWE: Highlights from the MANPOWER study

MANPOWER is an observational study in newly-diagnosed NAFLD patients with cardiometabolic comorbidities who were treated with EPL for 24 weeks where the effects of adjunctive EPL treatment on ultrasound and transaminases levels were evaluated from a real-world evidence perspective.[11]

Almost 75% of patients presented with simple steatosis. Obesity and increased body weight were found to be the most frequent comorbidities in NAFLD patients. However, of 2 827 patients only 13.8% adhered to the dietary and exercise advice given by their HCPs whereas over 90% adhered to EPL treatment.[11]

EPL use as an adjunct therapy was associated with:

- Ultrasound – proven significant improvement in liver hyperechogenicity after 3 and 6 months of treatment with EPL ($p<0.05$)
- Significant decrease of ALT, AST, GGT ($p<0.05$) observed at 3 and 6 months of treatment
- Significant improvement of lipid profiles ($p<0.05$) after only 3 months of treatment.[11]

RWE: real-world evidence; **EPL:** essential phospholipids; **NAFLD:** non-alcoholic fatty liver disease; **NASH:** non-alcoholic steatohepatitis; **T2DM:** type 2 diabetes; **WCHR:** waist-to-height ratio; **RCT:** randomized controlled trial; **ROC:** receiver operating curve; **Alk Ph:** alkaline phosphatase; **GGT:** gamma-glutamyl transferase; **ALT:** alanine aminotransferase; **AST:** aspartate aminotransferase; **AEs:** adverse events.

Importance of RWE in understanding the current disease landscape: MANPOWER results put into perspective

Intravenous EPL

Clinical studies (both trials and real world data) have been carried out with an intravenous form of EPL which provides 100% bioavailability. Between 1963 and 2018, in 23 studies >900 patients have been exposed to 15 483 days of intravenous EPL in courses of 7 days – 1 month. A very low incidence of AEs was reported. These studies showed rapid and significant decreases in ALT levels.[12-14]

References

1. Moon AM, *et al.* High mortality rates for SARS-CoV-2 infection in patients with pre-existing chronic liver disease and cirrhosis: Preliminary results from an international registry. J Hepatol. 2020;73:705–8.
2. Zhang C, *et al.* Liver injury in COVID-19: management and challenges. Lancet Gastroenterol Hepatol. 2020;5:428–30.
3. Zhou YJ, *et al.* Natural course of nonalcoholic fatty liver disease in southern China: a prospective cohort study. J Dig Dis. 2012;13:153–60
4. Hernaez R, *et al.* Diagnostic accuracy and reliability of ultrasonography for the detection of fatty liver: a meta-analysis. Hepatology 2011;54:1082–90.
5. Charatcharoenwitthaya P, *et al.* The spontaneous course of liver enzymes and its correlation in nonalcoholic fatty liver disease. Dig Dis Sci. 2012;57:1925–31.
6. Data on file
7. Shipovskaya AA & Dudanova OP. Intrahepatic cholestasis in nonalcoholic fatty liver disease. Ther Archive. 2018;02:69–74.
8. Dajani AI & Popovic B. World J Clin Cases, article in press.
9. Zhiguo L. Efficacy of polyene phosphatidylcholine in combination with metformin for diabetes complicated with non-alcoholic fatty liver disease. Inner Mongolia Journal of Traditional Chinese Medicine. 2013 No. 31.
10. Puri P, *et al.* A lipidomic analysis of nonalcoholic fatty liver disease. Hepatol. 2007;46:1081–90.
11. Maev IV, *et al.* Real-world comorbidities and treatment patterns among patients with non-alcoholic fatty liver disease receiving phosphatidylcholine as adjunctive therapy in Russia. BMJ Open Gastro. 2019;6:e000307.
12. Nan J. Clinical analysis of essentiale treatment of 90 patients with non-alcoholic fatty liver. Guide of China Medicine 2009;9:249–50.
13. Guo X-L, *et al.* Comparison of efficacies of diammonium glycyrrhizinate and polyne phosphatidylcholine on nonalcoholic steatohepatitis. Chinese Journal of New Drugs. 2012;21:1-7.
14. Zhou S-Y & Sun Z-Y. Observation of efficacy of polyene phosphatidylcholine in the treatment of fatty liver. J Clini Hepatol. 2010;26:1-4.

RWE: real-world evidence; **EPL:** essential phospholipids; **NAFLD:** non-alcoholic fatty liver disease; **NASH:** non-alcoholic steatohepatitis; **T2DM:** type 2 diabetes; **WCHR:** waist-to-height ratio; **RCT:** randomized controlled trial; **ROC:** receiver operating curve; **Alk Ph:** alkaline phosphatase; **GGT:** gamma-glutamyl transferase; **ALT:** alanine aminotransferase; **AST:** aspartate aminotransferase; **AEs:** adverse events.

Importance of RWE in understanding the current disease landscape: MANPOWER results put into perspective

Key learnings:

Appreciate the difference between RWE and clinical trials, example of the registries for COVID-19 patients with pre-existing CLD.

Ultrasound can be used to diagnose NAFLD, it is as reliable as histology in detecting steatosis 2–3 grade in NAFLD patients.

The St-index is a new non-invasive screening scale that can be used when NAFLD is suspected.

EPL are discussed. Their mechanism of action in steatosis and the most recent clinical evidence from their use in NAFLD is shown. Highlights from the MANPOWER study emphasize their efficacy in RWE.

Main take aways:

NAFLD generally and steatosis in particular are related to increased cardiovascular mortality.

Detecting liver hyperechogenicity by ultrasound imaging is one of the most important criterion to diagnose NAFLD: ultrasound in comparison with histology is an accurate and reliable method to detect steatosis.

ALT and AST levels do not reflect steatosis, dynamic changes of fibrosis, or even correlate with histological inflammation activity in NAFLD/NASH.

In more than 80% of patients with NAFLD and cardiometabolic comorbidities , steatosis severity can be reduced by adjunctive treatment with EPL, as recently confirmed in the RWE MANPOWER study.

1st GLOBAL LIVER HEALTH FORUM

SANOFI

MAT-GLB-2003464