ISG Masterclass – NASH – Current and Emerging Treatment

Answers to the Questions– Prof. Ajay Duseja

Definition/ Pathophysiology

1. Should NAFLD be replaced by MAFLD now.
    a. More discussion and consensus required for changing the terminology.
2. How relevant is lean NASH outside West Bengal.
    a. In our clinical practice it is around 10-15%. Would vary from population to population, rural/urban areas.
3. How to differentiate NASH and ASH
    a. Usually based on history of alcohol, MCV, AST/ALT ratio. Mayo clinic has given an index called ANI (Alcoholic/non-alcoholic steatohepatitis index) and is available free on their website.
4. What proportion in ICON-D cohort was without metabolic risk factors?
    a. Interim data of 2046 patients of ICON-D was presented at APDW-2019. Of these metabolic risk factors data was available in 1800 (88%) patients. At least one metabolic risk factor was present in 1616 (89%) patients.
5. Which patients with fatty liver on USG are at risk of progression
    a. Patients with older age, post-menopausal females, presence of diabetes mellitus, obesity or metabolic syndrome are at higher risk of progression. Patients with AST/ALT ratio>1, Low platelet count, high APRI, FIB-4, NFS and high LSM ($\geq$8 kPa) are presumed to have significant liver disease.
6. Is fatty liver with raised transaminases more likely to progress in comparison to those with normal enzymes.
    a. Yes, some data to suggest.
7. Association of NAFLD with sarcopenia
    a. Sarcopenia has been shown to be associated with the presence and severity of NAFLD
8. What proportion of cryptogenic cirrhosis are due to NAFLD.
    a. Most of the data on this issue is available on explant studies or case control studies. Variable figures suggest 20-50% of patients with cryptogenic cirrhosis are related to NAFLD.

Diagnosis

9. Should patients found to have fatty liver on USG be staged.
    a. Yes, all patients with suggestive of fatty liver on USG should be staged initially by non-invasive assessment and by liver biopsy if indicated.
10. Should we check for occult B and C in NAFLD.
    a. Not recommended routinely, unless indicated clinically in a given patient.
11. Serum ferritin and Auto-antibodies in NAFLD.
    a. Some studies have used serum ferritin levels as a biomarker for NASH amongst patients with NAFLD. Data has shown auto-antibodies to be positive in around 25% of patients as an epi-phenomenon. But if clinical and lab parameters are suggestive of AIH, it should be excluded by doing a liver biopsy.

12. Minimum tests before starting empirical treatment for NASH.
    a. Assess for the presence of diabetes mellitus, obesity and metabolic syndrome. Look at the AST/ALT ratio, platelet count, APRI, FIB-4, NFS and LSM before taking the decision to start pharmacotherapy in the absence of liver biopsy
13. Role of Fibroscan in NAFLD
    a. LSM $\geq$8 kPa is usually taken as evidence of significant fibrosis in NASH. Lot of original articles and few metanalyses available. Please refer to recent meta-analysis on CAP (Karlas T et al. Individual patient data meta-analysis of controlled attenuation parameter (CAP) technology for assessing steatosis. J Hepatol. 2017;66(5):1022-1030)
14. Role of liver biopsy in the era of Fibroscan
    a. All patients initially should be evaluated non-invasively. Those suggestive of NASH on non-invasive assessment should be advised liver biopsy. If not willing or liver biopsy contraindicated, can be treated with pharmacotherapy in addition to lifestyle interventions.

Treatment

15. Role of intermittent fasting in NASH
    a. Preliminary data shows it to be effective. More data required.
16. Keto diet in NASH
    a. Controversial data in NASH. Not recommended yet.
17. Which oil, ghee or butter for NASH
    a. Avoid saturated fats, hydrogenated oils and trans-fat. Beneficial effects shown by the use of olive oil.
18. Role of anti-obesity drugs like orlistat and pheniramine
    a. Limited data. Not recommended
19. Should we use UDCA in NASH
    a. Not recommended because of absence of histological improvement in clinical trials.
20. Is there a RCT of use of Pioglitazone in patients with diabetes mellitus.
    a. Yes, data is available regarding use of Pio in diabetes e. g. Bril F et al. Response to Pioglitazone in Patients With Nonalcoholic Steatohepatitis With vs Without Type 2 Diabetes. Clin Gastroenterol Hepatol. 2018;16(4):558-566.
21. Treatment of NASH without liver biopsy
    a. On case to case basis, these patients if are predicted to have NASH on non-invasive assessment can be treated with pharmacotherapy in addition to lifestyle interventions.
22. Duration of Saroglitazar and Vitamin E
    a. In the phase III study completed in India and the results presented in APASL 2020, Saroglitazar was used for one year. Vitamin E was given for 96 weeks the PIVENS study. However, in our clinical practice, we do not use vitamin E at a stretch for more than 6 months.
23. Can we give Saro without liver biopsy
    a. On case to case basis, these patients if are predicted to have NASH (F1-3) on non-invasive assessment can be treated with pharmacotherapy in addition to lifestyle interventions (If not willing for liver biopsy or contraindicated)

24. How to choose between Vitamin E and Saroglitazar
    a. Both drugs can be used in patients with biopsy proven NASH with F1 -3 fibrosis. However, the choice would go in favor of Saro in patients with diabetic dyslipidemia. Cost of the drug may be another consideration.
25. Can saroglitazar be used in Lean NASH
    a. Yes, if non-invasive assessment or liver biopsy suggestive of NASH with F1-3 fibrosis.
26. Can I use Lipaglyn for NASH patients
    a. Saroglitazar in the diabetic circle initially was marketed as Lipaglyn by the manufacturers. So if clinically indicated Saro can be used in NASH but the dose has to be 4mg/day.
27. Is there any prospect of Saroglitazar in NASH cirrhosis.
    a. No data available yet.
28. Is combination therapy better in NASH
    a. Clinical trials are exploring the combinations by targeting multiple pathways involved in the pathogenesis of NASH. Some however have failed.
29. Role of obeteicholic acid
    a. Based on the positive interim results of the phase III study (Regenerate trial), the manufactures are asking for approval.
30. How in a lifelong disease – 6mo or 1 year treatment would be effective
    a. Like in most chronic liver diseases, the aim of using pharmacotherapy in patients with NASH is to reduce the inflammation and fibrosis and prevent the progression to cirrhosis by using drugs for a finite period. NASH being a lifestyle disease, lifestyle modifications need to continue for long.
31. Interval of repeating LFT and Elastography in those on treatment
    a. We tend to monitor LFT at 3 monthly interval and Elastography annually.
32. Role of pharmacotherapy once the patients goes into decompensation.
    a. No data available on use of pharmacotherapy for NASH related decompensated cirrhosis. Data however is available in compensated cirrhosis
33. Will same drugs work in post-transplant NASH
    a. No data available on current drugs in post-transplant patients.
34. Utility of aspirin in NASH in patients taking it for CVD
    a. Preliminary data to suggest that aspirin may reduce hepatic fibrosis in NASH. Require more data.
35. Role of coffee in NASH
    a. Many studies including meta-analysis have shown beneficial role of coffee in reducing hepatic fibrosis. But most of the studies are cross sectional or case control.
36. Role of FMT in NASH
    a. There are on-going clinical trials.
37. NASH and Metabolic surgery
    a. Bariatric surgery – not recommended for primary treatment of NASH. However, can be done for obesity if otherwise indicated. NASH has been shown to improve with bariatric surgery.

38. Bariatric procedure for severe NASH or compensated cirrhosis.
    a. Bariatric surgery is not recommended for the treatment of NASH. However, if otherwise indicated for obesity and metabolic surgery, can be done in patients with severe NASH. Morbidity and mortality with bariatric surgery is higher in patients with cirrhosis.
39. Should you take liver biopsy in a suspected NASH cirrhosis undergoing bariatric surgery and avoid surgery if found to be cirrhotic/high fibrosis.
    a. Yes, liver biopsy should be taken at the time of bariatric surgery with or without the suspicion of high fibrosis/cirrhosis. Enough data is available on patients found to have incidental cirrhosis at the time of undergoing bariatric surgery. Morbidity and mortality after bariatric surgery have been found to be higher in cirrhosis in comparison to those without cirrhosis. The decision to avoid the surgery may have to individualized after discussion with the family.
40. Special treatment for Lean NASH
    a. No special treatment. Regular exercise has been shown to improve insulin sensitivity.