

Here are some news from the AGA Digestive Disease Week, held this year in New Orleans. We want to summarise a few clinical abstracts, which were all selected for oral or poster presentations during the core meeting. The largest clinical interest came this year from the HCV research field. S. De Maeght

1. COST-EFFECTIVENESS OF EPOETIN ALPHA FOR THE MANAGEMENT OF ANEMIA DURING HEPATITIS C COMBINATION THERAPY

Two oral presentations emphasise the future potential role of epoetin alpha (EPO) during classical HCV bitherapy to augment the SVR rate. Indeed anemia is a common adverse effect of HCV bitherapy and maintaining an optimal dose of Ribavirin will enhance SVR. Recent studies demonstrate that a significant proportion of patients treated with EPO experience improvement in anemia and are able to maintain RBV levels >800mg/d. Maintenance of higher RBV levels has been associated with improved SVR rates in geno 1 infected patients.

A. Post's team try to determine the cost-effectiveness of EPO for the management of anemia under peg-bitherapy for genotype 1 patients. EPO use was compared in a decision model to RBV dose reduction strategies in those patients experiencing clinically significant anemia (Hb drop >3g/dl after 4 weeks of bitherapy). These patients received either EPO for 4 weeks (followed in RBV dose reduction in EPO non responder) or a classical step-wise decrease in RBV dose. Non-responders to dose reduction in either group had combination therapy discontinued.

Conclusions:

1. EPO use is associated with a significant improvement in SVR compared to a RBV dose reduction strategy (SVR 61% vs 46%).
2. However the additional costs to obtain this improved response rate appear high (incremental cost-effectiveness ratio of 202 043 \$ per each additional SVR).

2. SUPERIOR EFFICACY OF TWICE A WEEK ADMINISTRATION OF PEGINTERFERON ALFA-2B PLUS RIBAVIRIN IN OBTAINING SVR IN HCV GENOTYPE 1

Because once a week administration of pegIFN alfa-2b produces an exponential decrease of IFN level, almost undetectable at Day 6 and 7, **Lodato's team** evaluates whether twice a week pegIFN alpha2b administration (with Ribavirin) may improve SVR, compared with the classical once a week pegylated bitherapy.

66 HCV patients were enrolled, 22 (68% genotype 1; 32 % geno 2) received pegIFN alfa 2b once a week and 43 (60% genotype 1; 40 % geno 2) received pegIFN alfa 2b twice a week. pegIFN dose were 1.5 and 2.4 mcg/kg/week. Both group received ribavirin 11 mg/kg/day and were comparable for rate of naive patients, genotype 1 (63%), sex ratio and age. Genotype 1 patients were treated for 48 weeks, and geno 2 for 24 weeks.

Results: For genotype1, twice a week treatment gives a higher SVR (46% vs 27%, p=.03) and among naive patients, twice a week treatment gives a higher SVR (72% vs 25%, p=.02) for all genotypes. Drop out rates were 32% and 19% for once and twice a week groups respectively.

Conclusion 1. Twice a week administration of alfa 2b pegIFN seems to be more effective than once a week in genotype 1 patients.

2. Tolerability and adherence was higher in twice a week administration group, possibly due to a more stable and continuous drug exposure.

3. THE EFFECTIVENESS OF PEGYLATED-INTERFERON AND RIBAVIRIN COMBINATION THERAPY FOR CHRONIC HEPATITIS C IN AN URBAN CLINIC SETTING COMPARED TO PIVOTAL CLINICAL TRIALS

In this study, **TC Johnson** et al presented a comparison of the pegylated bitherapy virological efficacy, in the *real life* compared to the large registration trials. Interestingly they also realised a comparison of the two available pegylated alfa interferons (pegIFN) (each with usual ribavirin bitherapy). It's the first time this kind of comparison was performed, originating from exactly the same group of patients, even if not randomly distributed. They retrospectively reviewed all naive patients' charts who were not treated in any clinical trials during 16 consecutive months.

There were 90 patients (57M:33F) in the study cohort. 74% genotype type 1, 25% type 2-3. 77% had liver biopsies (30% bridging fibrosis and 13% cirrhosis). The proportion treated with pegIFN alfa-2a or 2b was 44% and 56% respectively. Mean pre-treatment HCV RNA for genotype 1 patients treated with pegIFN alfa-2a and 2b were 1,640,000 IU/ml and 1,730,000 IU/mL ($p=0.9$).

Conclusions: 1. There was a decrease in the proportion of patients achieving an EVR in this clinic setting compared to those seen in the registration trials: Early viral response (EVR) at 3 months under therapy was 60% (63% and 58% for pegIFN alfa-2a and 2b respectively ($p=0.7$). EVR for genotype 1 patients were 63% and 51% respectively ($p=0.4$)

EVR for genotype 2-3 treated with pegIFN alfa-2a and 2b were 70% and 78% ($p=1.0$).

2. Type of pegylated interferon used in the combination treatment with ribavirin did not affect EVR in these naive HCV patients managed in a non-clinical trial setting. SVR results should be available for AASLD meeting.

4. DOES NON-ALCOHOLIC FATTY LIVER DISEASE(NAFLD) AND ITS RISK FACTORS AFFECT THE PROGRESSION OF FIBROSIS IN HCV PATIENTS?

Cross sectional studies suggest that the co-incidence of chronic HCV infection and NAFLD risk factors as obesity, type II diabetes mellitus (DM), hyperlipemia and hypertension (HT) could increase the risk to develop advanced fibrosis stages.

E. Schiff's team tried to confirm this assessment and therefore retrospectively reviewed records of 60 HCV patients who underwent at least 2 liver biopsies, which were blinded reviewed. The Scheuer-fibrosis and Brunt-steatosis scores were performed and related rates of progression were calculated.

60 patients were included with sex ratio 2.2, mean age 56 y and BMI 28 kg/m². The mean interval between biopsies was 3.7 y. 27% pts had HT, 12% DM and 28% hyperlipemia. None were active alcohol drinkers but past history of alcohol habits was reported in 22% (>50g/d) and 23% (<50g/d). Steatosis was reported in 38%.

HTA patients showed a fibrosis progression rate of 1.1, versus 0.2 in normotensive patients ($p=.01$). No significant relationship was found between DM, hyperlipemia or high BMI and progression of fibrosis rate.

Conclusions:

1. HT seems to be an independent predictor for the progression of HCV related fibrosis.

2. It is not the case with the others NAFLD main risk factors.

3. Steatosis was not identified in this study as an independent risk factor for progression of HCV fibrosis.

5. DARBEPOETIN ALFA (DA) FOR RIBAVIRIN-INDUCED ANEMIA IN PATIENTS WITH CHRONIC HEPATITIS C (CH-C) TREATED WITH PEGYLATED INTERFERON AND RIBAVIRIN (PEG-IFN/RBV): A PRELIMINARY ANALYSIS

Darbepoetin (DA), a novel long-acting erythropoiesis-stimulating protein, was given in an open label study with peg-bitherapy, if Hb fell <10.5g/dl. Initial dose (3 mcg/kg every-two-weeks) was titrated to target Hb 12 g/dl. 39 patients were studied (initial values: Hb 14.7 +/-1.2 g/dl, RBV dose 1051mg/d +/-198, 64% geno 1, age 48, 56% male). By week 12, 60% and 26% experienced Hb decline to <12 and 10.5 g/dl respectively. 33% required DA. Of those requiring DA, 77% did so before week 12. Under 6 weeks DA therapy, mean Hb increase was 1.3g and 83% patients maintained their intended RBV dose. After 8 weeks of DA associated tri-therapy, clinically significant health-related QOL improvements were noted. No significant toxicity related to DA has been noted.

Conclusions:

1. DA improves significantly anemia and HRQOL.
2. DA allows optimal RBV dose maintenance.

6. COST-EFFECTIVENESS OF PEGINTERFERON A-2B PLUS RIBAVIRIN TREATMENT OF CHRONIC HEPATITIS C WITH F1 FIBROSIS

Wong, Poynard, Manns, McHutchinson, Harvey and Albrecht have realised this study, not yet performed for the pegylated bitherapy, and more specially for histologically mild F1 study. Using data from Manns study, and UNOS, SEER and NIH data, they compared no antiviral therapy to pegIntron + >10.6mg/kg RBV. Observed SVR rates for metavir F1 patients were 63% overall (52% for geno1 and 91% for geno 2-3).

Conclusions:

1. Cost effectiveness ratios for treatment are largely cost-effective, even for those patients with F1 fibrosis, with \$5100 per discounted quality-adjusted life year gained overall (\$9,000 for geno 1 and \$400 for geno 2-3).
2. Pegylated bitherapy reduced the 20 y incidence of cirrhosis from 20% to 7.6% overall (to 10% for geno 1 and to 2% for geno 2-3).
3. It extended life expectancy by 2.3y overall (1.9 y for geno1 and 3.4 y for geno 2-3).
4. Quality adjusted life expectancy benefits of treatment were 5 y overall (4 y for geno1 and 7 y for geno 2-3).
5. It reduced the future cost of hepatitis complications by \$27,500 overall (\$22,900 for geno 1 and \$40,100 for geno 2-3).

7. HEPATITIS C COMBINATION THERAPY WITH VIRAMIDINE AND PEGINTERFERON ALFA-2A REDUCES POTENTIAL FOR RIBAVIRIN-RELATED HEMOLYTIC ANEMIA

and

8. CLINICAL STUDY OF VIRAMIDINE IN TREATMENT OF HEPATITIS C SUPPORTS RBC-SPARING MECHANISM OF ACTION.

The same group had two abstracts selected for oral presentations in plenary session about viramidine (VRM), a pro-drug of RBV.

VRM has been shown to target liver cells rather than red blood cells, suggesting it may have less haematological toxicity than RBV, and therefore could become the new standard in pegylated bitherapy.

This ongoing dose-ranging study compares VRM and RBV in combination with pegasys and evaluates the effect of treatment on Hb levels and on anti-viral activity. 180 patients were randomised in a 1:1 ratio to receive classical pegasys dosage with VRM 400, 600, or 800 mg bid or RBV 1-1.2 g daily.

Conclusions:

1. Haemolytic anemia (>2.5g/dl decrease from baseline) occurs less often with VRM 400-600 bitherapy (48% vs 82%), with no instance of Hb <10g/dl in VRM 400-600 groups (0% vs 24%).
2. Hb fall <10 g/dl in RBV group has a gender-based difference: 19% in male vs 38% in female.
3. 13% of RBV treated patients underwent dose reduction or discontinuation vs 0% in VRM group.
4. Others adverse events were similar, as were HCV RNA responses (24 months interim analysis).
5. At weeks 4, the RBV concentrations (C_{min}) in red blood cells were 126 mcg/ml for VRM600 group vs 246 mcg/ml for RBV group. At week 12, values were similar (159 vs 235 mcg/ml), with an identical virological response at interim analysis. It is consistent with the liver-targeting/red blood cell-sparing mechanism of action of this new pro-drug.

9. END OF TREATMENT RESPONSE FOR PEG-IFN + WEIGHT-BASED RIBAVIRIN NONRESPONDERS RETREATED WITH IFN ALFACON-1 + WEIGHT-BASED RIBAVIRIN

Two abstracts gave information about new treatment possibilities for pegIFN bitherapy non-responders patients.

It is a retrospective review of 137 consecutive previously non responders to peginteron-rebetol at week 12. They were immediately re-treated, with no washout period, with daily IFN alfacon-1 (15mcg sc) and weight-based rebetol. After a 12week period, in case of RNA negativation, the alfacon dosage was reduced to 15 mcg sc tiw for the remainder of the 48 weeks (if no RNA negativation, the alfacon bitherapy was continued at the same initial dosage).

Therapy was well tolerated. Fatigue and flu-like were reported in most patients, but none discontinued therapy. 16% had neutrophil count below 750 and required growth factors preventively.

At week 48, end of treatment response was 43%, for these initially-non-responder patients. SVR rate should be available for AASLD meeting.

10. SUCCESSFUL RETREATMENT OF PEGINTERFERON NONRESPONDER PATIENTS WITH CHRONIC HEPATITIS C WITH HIGH DOSE CONSENSUS INTERFERON INDUCTION THERAPY

50 patients initially non-responders to pegylated bitherapy were included (46 geno 1, 4 geno 4, 13 with bridging fibrosis or cirrhosis). They received alfacon at a dosage of 9 mcg/d for 16 weeks or 27 mcg/d for 4 weeks, followed by 18 mcg/d for 12 weeks. Thereafter treatment was continued in all groups with alfacon 9mcg/d and RBV 10-15 mg/kg/g for a new 34-56 weeks depending the PCR results, in view to assure a negative PCR result for at least 48 weeks under therapy.

Sustained virological response rates were 24% and 30% for 9mcg and the 27-18mcg groups respectively.

11. LIVER STEATOSIS IN CHRONIC HEPATITIS C. THE IMPORTANCE OF CO-FACTORS: BMI, ALCOHOL, LIPIDS AND SERUM MARKERS OF IRON STORAGE.

85 HCV patients with no alcohol consumption above 40 g/d, no diabetes mellitus (DM) or other viral hepatitis were studied for BMI, light alcohol consumption, and histological and biological parameters. There was 62% male, 69% genotype 1, 24% genotype 3, and BMI was <25 in 62% and >30 in 7%. Alcohol, even in small quantities, favoured more severe steatosis, present in 60%, vs. 28% of abstinent (p. 02). Steatosis was found in 64% but mild in 52%. The more severe steatosis was related with more severe fibrosis (p.002), with stage F3-4 in 67%. Even in the abstinent population, high ferritin levels were associated with more severe fibrosis and steatosis (p.03).

Conclusions:

1. steatosis seems an important determinant of liver fibrosis in chronic HCV, but is mild in the majority of patients.
2. Iron overload and alcohol in low doses (<40g/d) are important cofactors, associated with aggravation of steatosis and fibrosis.
3. Alcohol abstinence must be recommended, as it improves significantly the histological parameters of steatosis, and fibrosis.

12. Smoking is associated with increased fibrosis and vascular endothelial growth factor (VEGF) in patients with chronic hepatitis C (CHC).

Preliminary studies have suggested an association between cigarette smoking and an increased risk of developing liver fibrosis in CHC. Smoking causes hypoxia, and low oxygen concentrations induce the cytokines VEGF. Elevated levels have been observed in animal liver fibrosis models.

McHutchinson's team studied 170 viremic biopsied untreated chronic HCV patients. 25% were current smokers

Conclusions:

1. Cigarette smoking is significantly associated with higher Metavir fibrosis scores, which confirms previous reports suggesting an increased prevalence of hepatic fibrosis in chronic HCV patients who smoke.
2. VEGF levels were significantly associated with higher Metavir fibrosis scores. VEGF may be an additional factor in the molecular mechanisms of fibrogenesis.

13. NATURAL HISTORY OF ACUTE HEPATITIS C IN A U.S. COHORT

Records of 12 consecutive patients with acute HCV (ALT >10N, RNA positive and Ab seroconversion proved). 4 (2 with Bilirubin >2) were left untreated, with a 75% spontaneous seroconversion rate. 8 were treated (2 with Bilirubin >2, median time from first symptoms: 21 d), with also a 75% seroconversion rate. Spontaneous responders as well as treated patients who cleared the virus did so at a median of 64 d. Symptomatic patients with jaundice appear to be more capable of spontaneous clearance. Trials of immediate vs delayed treatment of acute HCV are mandatory.

14. THE EFFECTS OF WEIGHT AND LIFESTYLE CHANGES ON HYPERTRANSAMINASEMIA IN NONALCOHOLIC FATTY LIVER DISEASE: A LONGITUDINAL STUDY

Weight control and lifestyle changes are usually recommended as an initial step in the treatment of NAFLD. The specific efficacy of these recommendations was assessed. Prospective descriptive study of 1425 patients' longitudinal data. From these, 151 patients with elevated ALT, Ac HCV and Ag HBs negative, and alcohol consumption < 40 g/d. 87 patients showed ALT normalisation, under weight loss and lifestyle changes

Conclusions:

- 1.** ALT changes correlated significantly with body weight changes (p.0001). Losing >5% of body weight was associated with a greater proportion of ALT normalisation (82% vs 37%, p.004).
- 2.** Newly established regular exercise was associated with greater ALT improvement (-13 IU/L vs -2 IU/L, p.04).
- 3.** Alcohol restriction at any cut values (40, 80 or 140 g/week), or cessation of smoking was not associated with significant ALT improvement.
- 4.** During follow up, ALT remained normal in a significantly higher proportion of patients who maintained their body weight (body weight gain less than 5%) compared to patients who regained more than 5% weight (100% vs 17%, p.005).