**UE MRCE 2024**

**Cours « Essais randomisés »**

**Essai n°1 (2018)**

With the advent of highly effective oral therapy for hepatitis C virus (HCV) infection and the recent World Health Organization commitment, HCV elimination has become a realistic goal. However, in sub-Saharan Africa the HCV epidemic remains a neglected issue and access to care and treatment is almost inexistent. ANRS 12311 TAC is an international, phase IIb, open-label, non-randomized trial conducted in 120 treatment-naïve adults with confirmed genotype 1, 2 or 4 HCV infection.

The main eligibility criteria for participation in the trial were being at least 18 years old, having proven chronic HCV infection (third-generation ELISA IgG test) with genotype 1, 2 or 4 and HCV-RNA >12 IU/ml, no previous exposure to HCV treatment, agreement on using a contraceptive method 1-month prior treatment initiation and 7 months after treatment completion, weight between 40 and 125 kg and signed informed consent.

The following additional criteria applied for HIV-HCV-coinfected patients: HIV infection confirmed by fourth-generation ELISA and western blot, receiving stable antiretroviral treatment for at least 8 weeks, with two nucleos(t)ide reverse-transcription inhibitors (tenofovir or abacavir, and lamivudine or emtricitabine) and a third agent (raltegravir, lopinavir/ritonavir, atazanavir/ritonavir, darunavir/ritonavir, efavirenz), CD4 T-cell count >100 cells/µl and plasma HIV-RNA <200 copies/ml.

Non-inclusion criteria were as follows: positive HBsAg rapid test, known Child-Pugh B or C cirrhosis, pregnancy or breastfeeding, refusal of contraception, history of organ transplantation, comorbidities such as cancer (including hepatocellular carcinoma), epilepsy, drepanocytosis, myocardial infarction, QT elongation ≥20 ms, daily alcohol consumption >20 g (women) or 40 g (men), active drug use, hemoglobin <10 g/ml (women) and 11 g/ml (men), platelet count <50,000/µl, neutrophil count <750/µl, creatinine clearance with Modification of Diet in Renal Disease formula <50 ml/min, history of severe opportunistic infections in the previous 6 months and, for HIV-HCV-coinfected patients, history of non-adherence to antiretroviral treatment, and use of antiretrovirals other than those authorized in the trial.

Trial participants were divided into two treatment groups, one administered a 12-week treatment with sofosbuvir plus ledipasvir (for patients infected with genotype 1 or 4: SOF/LDV group, n = 80) and the other sofosbuvir plus weight-based ribavirin (for patients infected with genotype 2: SOF/RBV group, n = 40), and were then followed for 24 weeks (total trial duration: 36 weeks).

Following the WHO guidelines that were prevailing at the time the trial was designed, the aspartate aminotransferase-to-platelet ratio index (APRI) 18 was used to assess liver fibrosis, with values above 2 denoting cirrhosis.

The trial's primary endpoint was sustained virological response (SVR), assessed 12 weeks after the end of treatment, i.e. at week (W) 24.

Efficacy results showed an overall SVR rate of 89.2%, with no significant difference according to HCV genotype, and a satisfying tolerance profile, thereby supporting the use of sofosbuvir-based HCV therapy in the African context.

**Essai n°2 (2023)**

The combination of sofosbuvir, velpatasvir and voxilaprevir (SOF/VEL/VOX) is recommended for the retreatment of patients with HCV infection in whom previous direct-acting antiviral (DAA) treatment failed. However, whether ribavirin further increases the therapeutic efficacy of SOF/VEL/VOX retreatment remains unclear. We aimed to test this hypothesis in a randomized-controlled trial.

This RCT was conducted on 315 patients with chronic HCV who failed to respond to first-line DAA therapy, from December 2020 to December 2021. Patients were recruited from five specialized viral hepatitis treatment centers affiliated with the Egyptian National Committee for Control of Viral Hepatitis in three Egyptian cities (three centers in Cairo, one in Fayoum, and one in Damietta).

The sample size was calculated based on the results published by Zeuzem et al.,16 who found that SOF/VEL/VOX ± RBV is effective for the retreatment of patients who had experienced a prior DAA failure (with 93% achieving a sustained virological response 12 weeks after treatment end [SVR12]), and assuming a power = 0.80 and $\alpha = 0.05$. We used the PASS 11 sample size calculator which indicated 144 patients were needed in each group. Enrollment ended in June 2021 when 408 cases were enrolled and 315 cases were randomized, allowing for approximately 10% drop out.

This study included adult patients (≥18 years old) of both sexes who had chronic hepatitis C and detectable HCV RNA by PCR after completion of a previous DAA regimen and were eligible for antiviral treatment.

Exclusion criteria included patients with decompensated cirrhosis (Child-Pugh score B and C), patients with platelet count less than 50,000/µl, the presence of hepatocellular carcinoma or extrahepatic malignancy, and other contraindications related to study drug administration such as pregnancy, inability to use an effective contraceptive method, or lactation.

The participants were assigned randomly in a 1:1 ratio to receive either a fixed-dose combination of SOF/VEL/VOX (group A) or a fixed-dose combination of SOF/VEL/VOX with RBV (1,000 or 1,200 mg daily according to the patient's body weight: < or >75 kg) (group B); treatment duration was 12 weeks for both groups. Randomization was done centrally, and patients were assigned a randomization number created through a computer software program and distributed to centers through the study coordination team.

For all patients, full clinical history was recorded, including age, sex, weight, comorbidities and special habits of medical importance, then a thorough clinical examination was performed. Baseline laboratory evaluation was performed including liver profile (serum transaminases, serum bilirubin, serum albumin, prothrombin time and concentration), quantitative HCV RNA PCR, complete blood count, random blood sugar and glycosylated hemoglobin level for diabetic patients, serum creatinine level, serum alpha-fetoprotein level, HBsAg testing and pelvi-abdominal ultrasound examination.

Child-Pugh and Fibrosis-4 (FIB-4) scores were calculated. The FIB-4 can be used to categorize patients based on their estimated severity of fibrosis (FIB-4 <1.45, no/little fibrosis; FIB-4 >3.25, extensive fibrosis/cirrhosis).

The primary endpoint measurement was treatment efficacy. This was defined as the achievement of SVR12, as confirmed by undetectable HCV RNA on PCR 12 weeks after the end of treatment. Secondary outcome measurements were safety and tolerability. These parameters were assessed by a predesigned sheet for collecting reported adverse events, in addition to continuous monitoring of complete blood count, transaminases, bilirubin, and serum creatinine at baseline and every 4 weeks during treatment. Patients were required to attend centers on a monthly basis for clinical follow-up,

laboratory tests and refills of their medication. Compliance was verified by having patients return their empty drug containers at each visit.