Utility of testing for HCV Resistance Associated Variants (RAVs) to determine best Direct-Acting Antivirals (DAA) treatment regimen for treatment-naïve and re-treatment patients.

Alex Chipara[1], Benedict R S Rogers[1], Feza Kurmoo[1], Steve Kaye[3], Toby Delahooke[1], Martin J Wiselka[1,2], Julian W Tang[1,2]

[1]University Hospitals of Leicester NHS Trust, Leicester, UK; [2]University of Leicester, Leicester, UK; [3]Imperial College London, London, UK.

BACKGROUND: Currently in England, there is no recommendation for routinely testing for baseline hepatitis C resistance-associated variants (RAV)/substitutions (RAS). However, in certain patient groups, it is recommended in current Scottish, European and North American guidelines **[1,2,3].** To investigate the potential utility of baseline HCV RAV testing amongst treatment-naïve and treatment-experienced patients chronically infected with HCV, we submitted archived, retrospective and prospective pre-treatment samples for HCV RAV testing, to assess whether the presence of RAVs at baseline could impact on treatment outcomes.

METHODS: A case series of 11 patients (mean age 49.7 yrs, s.d. 12.67; 9 G1a: 2 G1b) were identified who exhibited baseline RAVs. Of these, only 3 were treatment-experienced. Baseline RAV testing was performed using an in-house sequencing method. Prediction of HCV drug susceptibility was determined using the geno2pheno algorithm (www.geno2pheno.org). In total, 71 NS5B, 68 NS5A, and 64 NS3 tests on 71 patient samples.

RESULTS: For each patient the full clinical and treatment history was available. Of the 9 G1a patients (mean age 47.35 yrs, s.d. 12.97), for NS3 (with the 174 mutations showing reduced susceptibility to telaprevir): 2 had 174S of which one also had 170V and the other 122N; 1 had 174B with 122G; 2 had both 80K (conferring resistance to simeprevir) and 174N; 2 had both 54S (conferring resistance to boceprevir) and 174N, of whom one also had 55I; 1 had 122N with 174S; 1 had 122G with 174B. For NS5A: 1 patient had both 30H and 93H, which confer resistance to NS5A inhibitors.

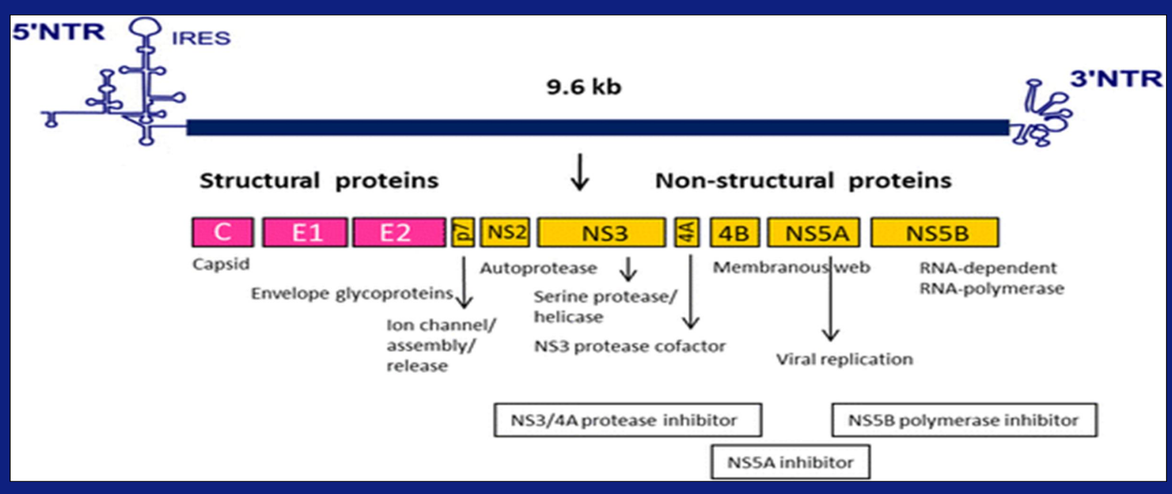
For the 2 G1b patients (mean age 59.03 yrs, s.d. 5.87), 1 had 80K and 170I (NS3) and 93H (NS5A); the other had 36M (which confers resistance to most NS3 protease inhibitors) and 31M and 93H (which confer resistance to most NS5A inhibitors).

One treatment-experienced (sofosbuvir-ledipasvir-ribavirin) G1b patient with NS5A baseline resistance (30H, 93H) had already started on Zepatier (elbasvir-grazoprevir), and might therefore be expected to fail therapy. One treatment-naïve G1b patient with NS5A baseline resistance (Y93H) had already started Epclusa (sofosbuvir-velpatasvir), and might therefore be expected to fail therapy.

DISCUSSION: Eight of the treatment-naïve patients showed NS3 RAVs compared to only one treatment-naïve patient with an NS5A RAV, raising the possibility of drug-resistant HCV circulating in the community (e.g. by contaminated needle sharing amongst intravenous drug-users, or inadequate sterilisation of needles by tattoo artists, etc.). Two cases with prior combination treatment were found to have extensive HCV RAVs affecting both NS3 and NS5A drug classes. In conclusion, baseline HCV RAV testing prior to NS5A-containing regimens is potentially useful in treatment choices, if it is shown in future to predict treatment failure, not just in treatment experienced patients but also those that are naïve to treatment.

Figure. Hepatitis C virus (HCV) genome, showing viral protein targets (i.e. NS3/NS4, NS5A, NS5B) for directly-acting antiviral (DAA) drug therapy. Drug name abbreviations used:

PEG-IFN – pegylated interferon
RBV – ribavirin
SOF – sofosbuvir
DCV – daclatasvir
LDV – ledipasvir
EBV – elbasvir
DAS – dasabuvir
RTV – ritonavir
SMV - simeprevir
BOC – boceprevir
TPV - telaprevir
GZV - grazoprevir
ASV - asunaprevir
OMB – ombitasvir
PTV – paritaprevir
VEL - velpatsavir



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CASE SUMMARIES: (treatment experienced- yellow; treatment-naïve - white)

Patient 1: 68/ F. HCV 1a. VL 249070IU/ml. Hepatocellular carcinoma. Previously rebounded after 12 weeks treatment on Harvoni and RBV NS5a mutations 30H, Y93H with resistance to DCV, EBV, LDV, OMB, VEL. Started on Epclusa (SOF/VEL). Latest VL 194768(13/7/17)

Patient 2: 55/ F. Treatment naïve. Smoker. Fibroscan F0/F1. Hemangioma segment 6 of liver on MRI. HCV 1b.VL 6663876IU/ml. NS3/4 mutations 80K, 170I with resistance to SMV and reduced susceptibility to ASV. NS5a mutation Y93H with resistance to DCV, EBV, LDV, OMB, VEL. Started on Zepatier (EBV/GZV) for 12 weeks on 22/08/17. Latest VL <12IU/ml (16/10/17) week 8.

Patient 3: 52/ M. Treatment naïve. Excessive alcohol 70+ units/wk. HCV 1a. VL 510244IU/ml. Fibroscan F4 compensated cirrhosis. Hepatomegaly with fatty infiltration. NS3 mutation 80K with resistance to SMV. Started Zepatier on 22/05/17. Current VL <12IU/ml (14/08/17).

Patient 4: 47/ M. Previous IFNRBV treatment 2005 in Spain, non-responder. Psoriasis. HCV 1a. VL 6389836IU/ml. NS3 mutation 174S with reduced susceptibility to TPV. Started Zepatier on 23/03/17. Latest VL <12IU/ml (25/10/17 which is not detected 3 months post EOT).

Patient 5: 38/ M. Treatment naïve. Previous IVDU. HCV 1a, VL 23882871. Fibroscan F0/F1. NS3 mutations 54S,55I,174N with resistance to BOC and reduced susceptibility to TPV. Was to be started on Zepatier and RBV but has been reported as lost to follow up.

Patient 6: 29/ M. Treatment naïve. HCV 1a. VL 1965325IU/ml. Fibroscan F0/F1. NS3 mutations 122N, 174S with reduced susceptibility to TPV. Started Zepatier and RBV on 10/07/17 for 16 weeks. Latest VL <12IU/ml (02/10/17)

Patient 7: 34/ M. Treatment naïve. HCV 1a. VL 28090IU/ml. Fibroscan F0/F1. NS3 mutation 80K with SMV resistance. Started on Zepatier for 12 weeks on 04/08/17. Latest VL <12IU/ml (29/09/17) week 8

Patient 8: 49 / M. Treatment naïve. HCV 1a VL 11805806IU/ml. NS3 mutations 54S, 174N with resistance to BOC and reduced susceptibility to TPV. Patient moved out of area before treatment.

Patient 9: 17/ M. Treatment naïve. Depression. HCV 1a. VL 204568. Fibroscan F0. Treatment naïve. Mutations in NS3 122G, 174B with reduced susceptibility to TPV. Started on Zepatier on 29/08/17 for 12 weeks.

Patient 10: 64/ M. Treatment naïve. Cirrhosis, metastatic prostate cancer. HCV 1a. VL 2234149IU/ml. NS3 mutations 170V, 174S with reduced susceptibility to TPV. Started on Zepatier and RBV for 16 weeks on 02/08/17. Latest VL <12iu/ml (24/10/17) week 12.

Patient 11: 63/ M. HCV1b.VL 647412IU/ml. Fibroscan F4. Compensated cirrhosis. Non-responder to PEG-IFN/Amantadine 1999, non - responder to PEG-IFN/RBV 2001, relapsed again after PEG-IFN/RBV/TPV 2013, relapsed after 12 weeks of SOF/LDV/RBV September 2015. NS3 (36M), NS5a (31M, Y93H) with resistance to BOC, TPV, DCV, EBV, LDV, OMB, VEL. Also has reduced susceptibility to ASV, GZV and SMV. Does not fit retreatment criteria set out by NHSE **[4]** therefore not eligible.

References:

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