Effect of Resistance Associated Substitutions on Retreatment of HCV infected patients with prior failure to Direct Acting Antiviral Therapy

Authors:

David Smith[1], Daniel Bradshaw[2], Jean Mbisa[2], Carmen Manso[2], David Bibby[2], Josh Singer[3], Emma Thomson[3], Ana Filipe[3], Elihu Aranday-Cortes[3], M. Azim Ansari[1], Anthony Brown[1], Emma Hudson[1], Jennifer Benselin[4], Brendan Healy[5], HCV Retreatment Group, STOP-HCV Consortium, HCV Research UK, John McLauchlan[3], Eleanor Barnes[1], Will Irving[4]

1. Peter Medawar Building for Pathogen Research, Nuffield Department of Medicine, University of Oxford
2. National Infection Service, Public Health England
3. MRC-University of Glasgow Centre for Virus Research
4. University of Nottingham and Nottingham University Hospitals NHS Trust
5. ?

Background and Aims:

5-10% of HCV-infected patients are not cured with interferon free Direct Acting Antiviral (DAA) regimes. These patients are now being retreated with pan-genotypic regimes such as sofosbuvir, velpatasvir and voxilaprevir, (SOF/VEL/VOX), SOF/VEL with ribavirin (RBV), or glecaprevir and pibrentasvir (GLE/PIB). Here, we present the first real world re-treatment data from the UK.

Method:

Blood samples were collected from 282 patients about to begin HCV retreatment. Next generation, deep, whole genome sequencing (WGS) was performed using target enrichment. HCV subtypes were assigned and NS3, NS5A and NS5B resistance associated substitutions (RAS) relevant to each genotype were identified (15% of reads cut off) using a bespoke pipeline developed for HCV-GLUE (hcv.glue.cvr.ac.uk).

Results:

Pre-retreatment WGSs were generated from 260 patients. Of these, 87% had previously received an NS5A inhibitor, 30% a protease inhibitor and 50% sofosbuvir. 64% of patients had cirrhosis with 26% decompensated, 11% had hepatocellular carcinoma and 9% had previously received a liver transplant. Subtypes 1a (41%, n=106) and 3a (39%, n=102) were the most common; the remaining sequences included 19 subtypes within genotypes 1,2,3,4 and 6. RAS to NS5A inhibitors were the most common polymorphisms, identified in 64% (n=167) of patients. RAS to Protease Inhibitors were found in 30% (n=78) and to NS5B Inhibitors in 5% (n=14). Retreatment outcomes are currently available for 53 patients (the remaining outcomes will be available by April 2019). 53% (n=28) of patients were retreated with SOF/VEL/VOX, 26% (n=14) received GLE/PIB and 21% (n=11) received SOF/VEL+RBV. The overall re-treatment SVR12 rate was 85% (45/53) ITT and 92% (49/53) PP; re-treatment

failures included 1 non–responders and 3 relapsers (4 cirrhotic, gt 1a, 3k, 4c), 2 patients lost to follow up, 1 was re-infected, 1 discontinued. SVR rates by re-treatment regime, subtype and presence of RAS pre-retreatment is shown (Figure 1). At the time of retreatment initiation, 37% of patients had RAS to the NS5A inhibitor they received as retreatment, 8% had RAS to the NS3 Inhibitor and 4% had RAS to sofosbuvir. There was no association with the presence of RAS and outcome (P=0.35).

Conclusions:

The SVR rate for the retreatment of patients with prior DAA therapy failure is high. Pre retreatment RAS are common but do not associate with re-treatment outcomes. Interestingly the two SOF/VEL/VOX failures were subtypes rarely found in the UK (3k and 4c).

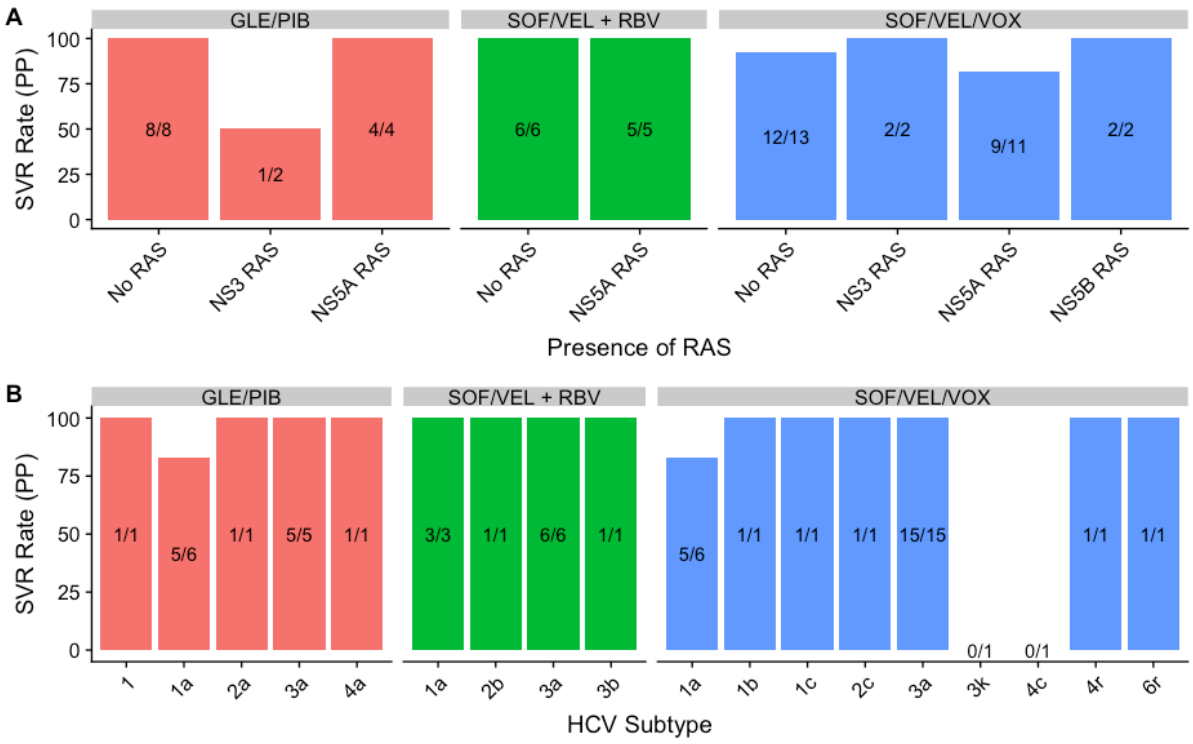

Figure 1: SVR12 rates for each DAA combination split by presence of RAS in each gene (A) or by HCV Subtype (B).