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activated memory phenotype and had a marked expansion of plasmablasts by W48. In parallel, ELISPOT data showed an increase in SPU against HBSAg in the 3 patients with HBSAg loss and anti-HBs by W48, confirming the recovery of antibody-producing functionality. **Conclusion**: Functional cure (HBSAg loss) and viral control following NA withdrawal associate with recovery of the low frequencies and poor functionality of HBV-specific B cells in CHB. These findings support further studies to explore the use of B cells as biomarkers of clinical outcome and as targets for further immunotherapeutic boosting.

**OS068**

**Enforced cytotoxic signature of HBV pol455-specific CD8+ T cells in chronic HBV infection**

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**Background and aims:** T-cell exhaustion represents a distinct T-cell differentiation program associated with chronic viral infections. Several studies have shown that exhausted CD8+ T cells are heterogeneous. In chronic HBV infection, we and others observed major differences in the phenotype and function as well as in the degree of dysfunction of HBV-specific CD8+ T cells targeting different antigens. The aim of this study was to investigate the molecular heterogeneity of HBV-specific CD8+ T cells targeting different antigens.

**Method:** To determine the subset diversification of HBV-specific CD8+ T cells targeting different antigens, we performed high-throughput single-cell RNA sequencing using CEL-Seq2 technology. We obtained HBVcore18- and HBVpol455-specific CD8+ T cells from HBeAg-negative chronically HBV-infected patients who endogenously control the viral infection as well as under NUC treatment. Phenotypic and functional analyses were performed after pMHC tetramer-based enrichment and peptide-specific expansion.

**Results:** Cluster analysis of single-cell transcriptomes revealed a different subset diversification of HBVcore18- versus HBVpol455-specific CD8+ T cells. In particular, HBVcore18-specific CD8+ T cells were mostly comprised of precursor/memory-like exhausted T-cell subsets. Within HBVpol455-specific CD8+ T cells, we could identify a cluster of cells that highly expressed cytotoxic genes including GZMB, PRF1, and NKG7 was also elevated in this subset. Interestingly, we further observed that the cytotoxic subset is restricted to HBVpol455-specific CD8+ T cells obtained from patients who endogenously control the viral infection indicating that the enforced cytotoxic signature may be linked to virological HBV control in these patients. The differential transcriptional profile of HBVpol455-specific CD8+ T cells was further confirmed ex vivo after pMHC tetramer-based enrichment. Indeed, at the protein level, we detected a terminal effector differentiation and higher cytotoxic effector capacity of HBVpol455-specific CD8 T cells obtained from treatment-naïve patients in comparison to patients requiring antiviral therapy.

**Conclusion:** In sum, our data highlight an enforced cytotoxic signature in HBVpol455-specific CD8+ T cells of treatment-naïve patients which may be related to virological control in these patients. This observation might have potential implications for the design of immunotherapeutic approaches in HBV cure.

**OS069**

**Humoral and cellular immune responses to SARS-CoV-2 vaccination across multiple vaccine platforms and liver disease types: an EASL registry multicentre prospective cohort study**

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**Background and aims:** Emerging data have demonstrated suboptimal immune responses to SARS-CoV-2 vaccination in immunosuppressed cohorts. However, unified assessments comparing multiple vaccine platforms across the spectrum of liver disease are lacking. We aimed to investigate humoral and cellular immune responses in patients across Europe with cirrhosis, autoimmune hepatitis (AIH), liver transplantation (LT), and vascular liver disorders using coordinated sampling timepoints and laboratory assays.
Method: Serum and peripheral blood mononuclear cells were collected for 792 and 283 patients respectively by the EASL COVID-Hep network and UK OCTAVE study across 4 European countries. Data for 93 healthy controls (HC) were derived from the UK PITCH consortium. Samples were taken <1-week before second vaccination (V2), 28-days post V2, and at baseline where possible. As of 28/11/2021, anti-Spike (S) and nucleocapsid (N) Ig titres (Roche) and Spike (V2), 28-days post V2, and at baseline where possible. As of 28/11/2021, anti-Spike (S) and nucleocapsid (N) Ig titres (Roche) and Spike (V2), 28-days post V2, and at baseline where possible. As of 28/11/2021, anti-Spike (S) and nucleocapsid (N) Ig titres (Roche) and Spike specific T-cell responses (IFN-γ ELISpot) were available in 151 and 75 patients respectively, and all controls. Ongoing analysis using proliferation, intracellular cytokine stimulation, tetramer, and AIM assays will define cellular function.

Results: In HC, two doses of BNT162b2 induced a 10-fold increase in median anti-S Ig titre compared to two doses of ChAdOx1 (15634 vs 1198 U/ml; p < 0.0001) (Fig 1A). LT recipients had diminished median anti-S Ig titres compared to HC after two vaccine doses of either BNT162b2 (169 vs 15634 U/ml; p < 0.0001) or ChAdOx1 (51 vs 1198 U/ml; p < 0.0001). Compared to HC, patients with cirrhosis had reduced anti-S Ig titres when vaccinated with BNT162b2 (1155 vs 15634 U/ml; p < 0.0001) but comparable titres when vaccinated with ChAdOx1 (1259 vs 1198 U/ml; p = 0.97). There was no difference in response to ChAdOx1 according to Child-Pugh class. Data was available for AH patients vaccinated with ChAdOx1 who had lower anti-S Ig titres compared to HC (443 vs 1198 U/ml; p = 0.0241). There were suboptimal antibody responses to a single vaccine dose across all disease groups relative to HC (Fig 1A). Seroconversion (anti-S Ig ≥0.8 U/ml) occurred in 100% of cirrhosis patients, 99.5% of AH, but only 70% of LT recipients versus 100% of HC (p < 0.0001). Four LT recipients receiving BNT162b2 were positive for N-protein antibodies and had elevated anti-S Ig compared to those negative for N-protein antibodies (25 000 vs 170 U/ml; p < 0.0001). T-cell responses were heterogeneous across all cohorts (Fig 1B) however a higher proportion of LT recipients failed to generate an IFN-γ response after V2 compared to HC (32% vs 10%; p = 0.0369).

Conclusion: LT recipients had markedly reduced antibody and T-cell responses to SARS-CoV-2 vaccination. Responses to BNT162b2 were significantly reduced in patients with cirrhosis compared to healthy controls. Ongoing analysis across the rest of the cohort will define SARS-CoV-2 specific T- and B-cell function.