

Elimination of Chronic Viral Hepatitis: What's New in 2021

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Citation: EMJ Gastroenterol. 2021;10[1]:19-22.



RECENT breakthrough research was shared and debated on Day 2 of the United European Gastroenterology (UEG) Week Virtual Congress 2021 in the symposium session discussing the progress towards, and barriers to, the elimination of chronic viral hepatitis (HCV). The session featured experts in the field, including Sabela Lens, Division of Infection and Immunity, University College London, UK, and Jean-Michel Pawlotsky, National Reference Centre for Viral Hepatitis B, C and Delta, Department of Virology & INSERM U955, Henri Mondor Hospital, University of Paris-Est Créteil, France, who came together to share knowledge, challenge findings, and contribute to the fundamental goal of HCV elimination. The symposium looked at all aspects of eliminating HCV, from profiling the disease in the clinic to large-scale epidemiological characteristics of HCV within global populations.

THE ROLE OF ADAPTIVE IMMUNITY IN CHRONIC HEPATITIS B INFECTION

The presentation was opened by up-and-coming expert Lens who shared her recent research investigating the changes chronic hepatitis B (CHB) infection induces in immune cells, specifically changes to the memory B cell compartment. B cells are important both for preventing initial infection but also for ongoing control of CHB. Lens's study sought to investigate the differences in phenotype of antigen-specific B cells between adult and paediatric patients with CHB. Paediatric patients often present with less exhausted B cells, so the research aimed to discover whether this was due to shortened duration of exposure to the antigen versus fundamental defects in antigen-specific development due to an

immature immune system or inadequacy of assistance from T follicular helper cells (cTfh).

The group performed flow cytometry for the *ex vivo* quantification of antigen-specific B cells, specifically s antigen-specific hepatitis B virus (HBV) B cells (sAgB) and core antigen-specific HBV B cells (cAgB), using stringent gating criteria to avoid non-specific binding. The study included groups of healthy children and adults alongside adults with CHB and paediatric patients with CHB. The study found circulating sAgB markedly reduced in children relative to adults with no significant difference in cAgB between the groups. Lens and her colleagues subsequently analysed HBV-specific B cells, classifying them into subsets based on the expression of markers CD27 and CD21. The absence of both markers

indicates an atypical memory B cell (atMBC) classification. Researchers found that this subtype was significantly expanded in sAgB cell population compared with cAgB cell population in children with CHB. Analysis on the global B cell stage of all study groups showed that this expansion of atMBC was only found in children with CHB and not in infected adults or either of the healthy control groups.

Further analysis of the atMBC cells, Lens explained, found increased expression of inhibitory marker CD22 and exhaustion marker PD-1 compared with classic memory B cell (cMBC) counterparts. Furthermore, chemokine CXCR5 and costimulatory molecules CD80 and CD40 expression was reduced in atMBC relative to cMBC in children with CHB. CXCR5 drives sequestration of B cells to the germinal centre in the lymph nodes where they interact with cTfh, and the costimulatory molecules drive this interaction. Notably, analysis of cTfh in children with CHB showed that CD40L, the counterpart costimulatory ligand to CD40, had reduced expression.

In her final remarks, Lens explained that low levels of sAgB and expanded atMBC in

analyse HBV-specific B cells in the liver and the role that they play in CHB disease.

COVID-19: THE IMPACT ON ELIMINATING CHRONIC VIRAL HEPATITIS

The symposium also featured a presentation from Pawlotsky, who chose to speak on a more epidemiological level about methods to success and barriers to achieving the elimination of HCV. The World Health Organization's (WHO's) current target is the elimination of viral hepatitis as a major public health concern by 2030. They classify elimination as meaning "a world where viral hepatitis transmission is halted and everyone living with hepatitis has access to safe affordable and effective care and treatment."¹

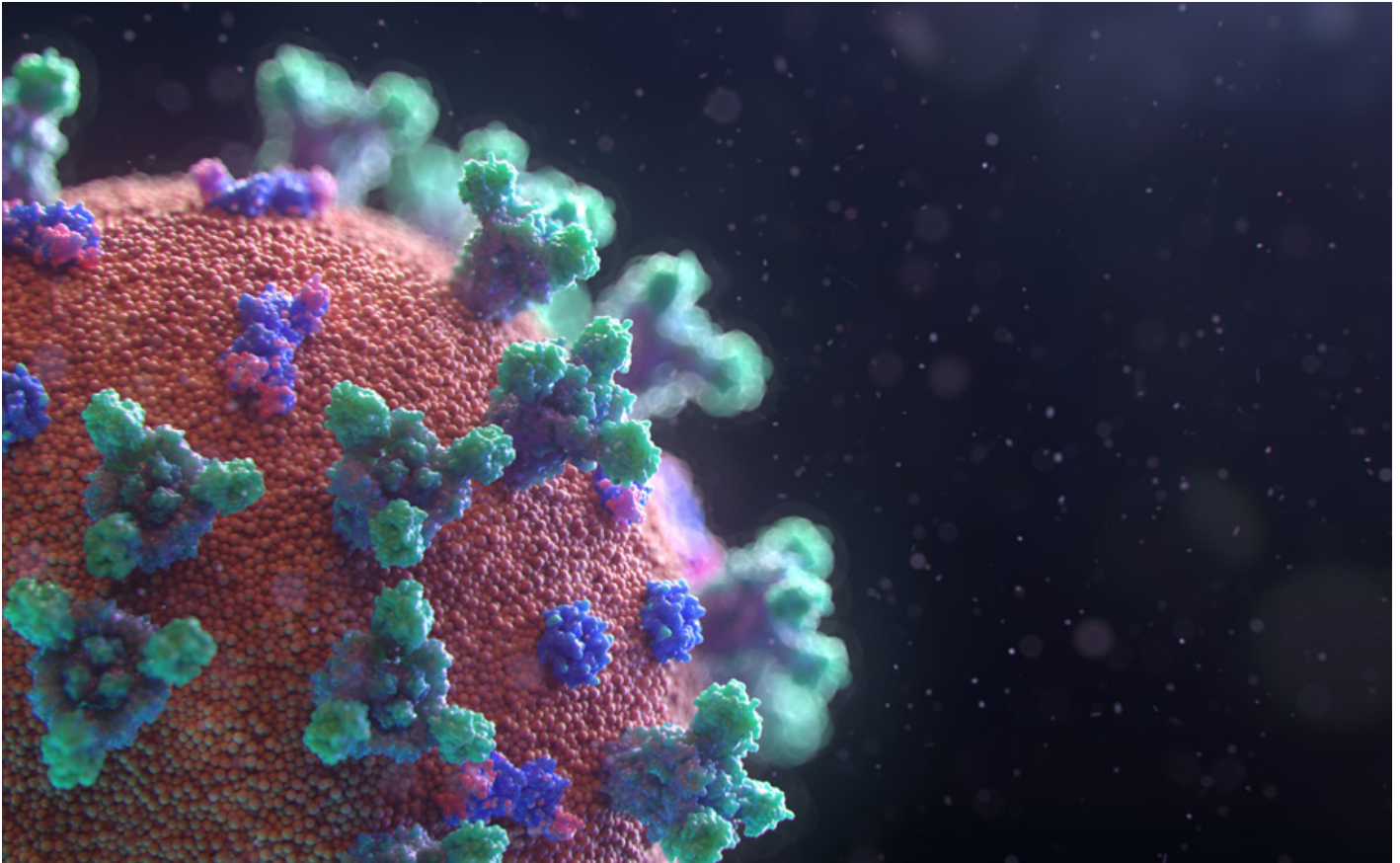
In coalition, representatives from global institutions, American Association for the Study of Liver Diseases (AASLD), the European Associations for the Study of the Liver (EASL), Asian Pacific Association for the Study of the Liver (APASL), and the Latin American Association for the Study of the Liver (ALEH) have given a joint call to action identifying four key areas to focus on

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children represent a difference from CHB disease expression in adults. Furthermore, reduced expression of co-stimulatory molecules and relocation cytokines required for the B-T cell interaction suggest inadequate T cell assistance accounting for the exhausted B cells with minimal antibody production observed in patients with CHB. These findings in particular point to a need to boost B cell stimulation in children with CHB to rescue humoral immunity. In the question and answer session after the presentation, the experts debated the findings of increased PD-1 expression, suggesting that treatment with PD-1 inhibitors could rescue some humoral responses through reducing cell exhaustion. Lens agreed, highlighting the need for further research and future study to

to achieve HCV elimination. These include simplification of diagnostic treatment and algorithms with a move towards the goal of a one-stop 'test-and-cure' for HCV; integration of HCV treatment with primary care and other disease programmes, such as HIV and tuberculosis; decentralisation of HCV service from large urban referral hospitals to local level care; and finally, task sharing of HCV care for uncomplicated cases with primary care clinicians, nurses, pharmacists, and trained community health workers.²

Pawlotsky's presentation reflected on the impact that the COVID-19 pandemic has had upon the goal of HCV elimination by 2030. The pandemic brought with it disruption to healthcare services that inevitably impacted



HCV treatment, through de-prioritisation of screening services, diversion of staff to COVID-19 response, and disruption to access for drug and harm reduction services. Overall, these changes to HCV care since March 2020 have led to a drop in the rates of screening, diagnosis, and linkage to care and treatment.

The impact of COVID-19 upon elimination goals has been examined in several studies as presented by Pawlotsky. A study analysing the use of ambulatory HCV testing at the Boston Medical Centre found a 50% drop in mean daily HCV antibody testing after 16th March 2020, compared to the previous year, with a 21% reduction in mean new cases identified.³ Issues have also arisen with drug utilisation throughout the pandemic. A retrospective study of direct-acting antiviral use across a number of countries found that the majority of countries had experienced a significant decrease in direct-acting antivirals sold from March to August 2020 compared with the same period of 2019.⁴

These findings beg the question of what the global impact of a 1-year delay to HCV elimination programmes will be. Modelling

studies have looked to the future to assess the fallout from changes to HCV healthcare provision. Pawlotsky communicated the findings of a study in which he participated that modelled for a 1-year delay in elimination programmes, finding that approximately 906,000 less diagnoses will be made between 2020 and 2030 as a result of COVID-19. The model suggested treatment commencement will diminish by 746,000, and there will be 623,000 additional viraemic infections that would not have happened if COVID-19 had never occurred. Pawlotsky also made the significant point that these models were based on 1 year of delays; however, as we have seen, the COVID-19 pandemic has persisted for much longer.

Pawlotsky closed his discussion by offering a contrasting point of view and drawing attention to the opportunities that the COVID-19 pandemic might offer for HCV elimination, emphasising the importance of not missing this moment to mitigate some of the consequential delays. The pandemic has brought with it increased awareness of infectious diseases, as well as an increased

usage and recognition of the value of telemedicine. There is also the potential to combine the testing, diagnosis, and treatment for COVID-19 and HCV. Opportunities for increased efficiency have been researched, with one team in Northern Italy analysing the potential for HCV detection through mass COVID-19 testing. Approximately 5,000 patients were tested for severe acute respiratory syndrome coronavirus 2, with half that number also being tested for HCV. Researchers identified 72 HCV antibody positive individuals who were subsequently linked to the necessary treatment.

Pawlotsky concluded his presentation with a call to action for researchers, funding bodies, and governments, emphasising that the tools and recipes were within reach to achieve the WHO goal of eliminating HCV as a public health threat. He summarised that “the COVID-19 pandemic has had, still has and will have a major negative impact on HCV elimination programmes.” However, the pandemic may also offer new opportunities to accelerate aspects of HCV elimination in the coming years and these must be exploited.

CONCLUDING COMMENTS

HCV is an infectious disease that remains persistent within populations. Achieving the goal of elimination would contribute positively to nations worldwide, both

socially and economically. This goal will only be reached by a combination of basic and clinical research combined with population-wide analysis of public health initiatives, treatment uptake, and mitigating environmental factors. Lens’s and Pawlotsky’s presentations both demonstrate a positive and hopeful look to the future. Lens’s research provides an example of the necessary steps to understand the virus and the immune responses it initiates to develop new and effective therapies. Pawlotsky’s summary of both the impact of the pandemic but also the potential opportunities it presents in helping to improve the future of HCV care demonstrates the holistic thinking needed to achieve elimination. ■

References

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