News in Brief

Conference on retroviruses and opportunistic infections (virtual): March 6—10, 2021

Liam J Messin*

EBioMedicine, 125 London Wall, London EC2Y 5AS, UK

ARTICLE INFO

Article History:
Received 20 May 2021
Accepted 20 May 2021
Available online xxx

Keywords:
HIV
AIDS
COVID-19
Retrovirus
Immunotherapy

ABSTRACT

The Conference on Retroviruses and Opportunistic Infections (CROI) for 2021 was, as with so many other conferences in the past 12 months, held online. CROI provided a forum for basic scientists and clinical researchers to bring together and discuss their work on human retroviruses and associated diseases, with HIV and SARS-CoV-2 being the two viruses most covered this year. Below are some examples of the work presented at the conference, highlighting both the innovative approaches to understanding and treating viral infections but also the breadth of topics covered.

© 2021 The Author. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)

1. HIV and comorbidities

One of the great success stories of modern medicine is the development of antiretroviral therapy (ART), which allows people with HIV to control the infection and have a better quality of life. However, ART is associated with side-effects, such as bone loss. Bone metabolism is controlled by the balanced actions of osteoclasts (that mediate bone destruction) and osteoblasts (that mediate bone construction). ART shifts this balance in favour of osteoclasts, resulting in bone loss and increased fracture risk for people with HIV. Tara McGinty (University College Dublin, Dublin, Ireland) presented data from a phase 4 clinical trial that aimed to ascertain the effect of oral bisphosphonate alendronate (BA), a generic medicine used to treat osteoporosis, on bone health in people with HIV undergoing ART. In the trial people with HIV received either BA or placebo 2 weeks before initiating ART for 14 weeks in total. After 14 weeks, hip bone mineral density (hBMD) increased in patients taking BA and remained above baseline (0-5%) 36 weeks later. This finding contrasted with patients taking placebo, who showed a steady decline in hBMD, with a final hBMD 2-47% lower than baseline after 50 weeks. With no severe side-effects of BA treatment, this study supports the use of this generic drug for patients initiating ART.

Comorbidities of HIV are not limited to changes in bone mineral density and people with HIV have increased mortality from non-HIV related comorbidities compared with people without HIV. Priscilla Hsue (University of California San Francisco, CA, USA) presented data from their study that applied large scale proteomics to identify new biomarkers to predict all-cause mortality in people with HIV. The plasma concentrations of almost 5000 proteins in over 1500 people with HIV were measured, and unique proteins were identified that were predictive of mortality in HIV even after adjustment for age, CD4 count, and HIV viral load. The top ten prognostic proteins included proteins involved with cell adhesion, immunity, cell growth, and coagulation. Five of these proteins have known therapeutic options and thus could be targets for the reduction of mortality in people with HIV.

Cardiovascular comorbidities and inflammation were also shown to be affected by birth sex. Samuel Schnittman (University of California San Francisco, CA, USA) presented a case-cohort study in which plasma samples were obtained from people with HIV after 1 year of ART-mediated virological suppression. The authors analysed plasma biomarkers in relation to incident cardiovascular disease events, including ischemic stroke, type 1 (T1MI) and type 2 (T2MI) myocardial infarctions, and venous thromboembolism (VTE). The study found that women had higher concentrations of 11 out of 13 inflammatory markers measured than men, and that these differences tended to be more pronounced among older participants. Although most biomarkers were associated with a higher risk of T2MI and all-cause mortality, only a subset were associated with other events: higher CRP, IL-6, LBP, suPAR, sTNFR1, sTNFR2, and CMV IgG titre were associated with a greater hazard of T1MI, and higher CRP, IL-6, LBP, suPAR, sTNFR1, and CMV IgG titre were associated with increased risk of VTE. No significant associations with ischemic stroke were identified. This association between inflammation and...
cardiovascular disease tended to be stronger in women than men, though the reverse was seen with VTE.

2. HIV and the nervous system

Alyssa Vecchio (University of North Carolina at Chapel Hill, NC, USA) presented data from their study that investigated the relationship between patient’s sex and ART-induced neurocognitive impairment. 83 people with HIV (43 [52%] women) on ART from rural Uganda were recruited and underwent neuropsychological assessment and lumbar puncture to extract cerebrospinal fluid (CSF). The overall concentrations of CSF inflammatory markers were not different between men and women. However, 11 (69%) out of 16 markers in male participants were found to correlate with neuropsychological outcomes (eg, IL-12p70 concentration correlated with patient score on a short-term memory test). Other markers in people with HIV, such as MIP-1β (CCL4), were positively correlated with several neuropsychological outcomes. CSF inflammation markers in women with HIV showed weaker correlation with neuropsychological outcomes.

Two talks presented the use of mitochondrial DNA (mtDNA) to predict neurocognitive impairment. Karen Volpe (Vanderbilt University Medical Center, TN, USA) presented work correlating neurocognitive score and mtDNA sequences for 744 people (357 of African ancestry and 317 of European ancestry). Potential deleterious mtDNA mutations were predicted using the MutPred algorithm. Surprisingly, mutated mtDNA appeared protective, with predicted deleterious mutations being associated with an improvement of motor activity in people with HIV. Dipesh Solanki (University of California San Diego, CA, USA) also presented findings relating mtDNA to neurological conditions. Solanki and colleagues took buccal swabs from 149 adults (124 [83-2%] people with HIV and 25 [16-8%] people without HIV) and, from these swabs, measured copies per cell (CPC) of both wild type mtDNA and mtDNA harbouring the common deletion mutation (mtCDM, a 4977 bp deletion removing parts of complex I, IV, and V preventing normal mitochondria function). CPC of wild type mtDNA and mtCDM were higher in people with HIV and greater CPC of wild-type mtDNA was significantly associated with higher CSF concentration of amyloid-β 1-42 (a precursor for the amyloid plaques that cause Alzheimer’s disease). These two studies indicate the complicated relationship between mtDNA status and neurocognitive impairment in people with HIV.

A potential future treatment for neurological damage in people with HIV was presented by Yoelvis Garcia-Mesa (University of Pennsylvania, PA, USA) who showed results on the potential protective activities of dimethyl fumarate (DMF), an FDA-approved anti-inflammatory drug. Garcia-Mesa and colleagues first tested DMF in Rhesus macaques (R macaques) infected with simian immunodeficiency virus (SIV, a close relative of HIV). The subset of R macaques fed DMF showed increased expression of protective antioxidants proteins (including GPX1, NQO1, HO-1, and PRDX1) compared with control animals. Fed animals also showed lower concentrations of proteins damaged by oxidation and less DNA damage in both the brainstem and frontal cortex. These results provide support for the further testing of DMF in people with HIV to protect against neurological damage.

3. Antibody production

There was also positive news concerning potential COVID-19 treatments at the conference. Both Myron Cohen (University of North Carolina at Chapel Hill, NC, USA) and Michael Dougan (Harvard Medical School, MA, USA) presented results showing the efficacy of antibodies in the treatment of COVID-19. Cohen presented findings from BLAZE-2, a phase 3 study examining the effect of bamlanivimab (a monoclonal antibody that binds to the SARS-CoV-2 spike protein) in reducing COVID-19 related morbidity and mortality in nursing homes in the USA. The study enrolled residents at nursing homes who had reported at least one previous COVID-19 case. To reach participants and comply with COVID-19 lockdown restrictions, their group used mobile research units and medical vans that travelled across the USA delivering equipment and personnel to patients. Participants received either intravenous bamlanivimab or a placebo. The impact was significant; approximately 25% of residents who received the placebo developed symptomatic COVID-19 compared with under 10% in participants who received bamlanivimab. The placebo group reported four (2-9%) deaths from COVID-19 compared with none in the Bamlanivimab group. Treatment with bamlanivimab also reduced symptoms in patients who were deemed high-risk, with participants who tested positive for SARS-CoV-2 showing a lower viral load if they were first treated with bamlanivimab. Dougan presented data from their study examining the effect of bamlanivimab (isolated from a US patient with COVID-19) combined with etesevimab (another monoclonal antibody, from a Chinese patient with COVID-19) as part of the BLAZE-1 phase 3 trial. This trial recruited 1035 high-risk ambulatory patients with mild-to-moderate COVID-19. Patients received either intravenous injections of bamlanivimab and etesevimab, or placebo, within 3 days of laboratory diagnosis. After 29 days, 7% of placebo patients had either COVID-19 related hospitalisation or death, compared to 2-1% of patients receiving the antibodies. There were no deaths in the treatment group, compared to 1-9% of patients in the placebo group. Treatment with both antibodies also resulted in decreased viral load in patients and faster resolution of symptoms.

Antibodies were also advocated as a treatment for HIV. Joseph Casazza (National Institute of Allergy and Infectious Diseases, MD, USA) presented data from a phase 1 open-label trial using a viral vector to engineer patient cells to produce their own broad neutralising antibodies against HIV-1. Eight people with HIV on ART with viral loads less than 50 copies per ml were given an adenovirus-associated virus (AAV8) vector containing a transgene encoding the broad neutralising antibody (bNAb) VRC07 by intramuscular injection. VRC07 binds the HIV-1 envelope, thereby preventing HIV infection. AAV8 enters the nucleus of human cells where the transgene does not integrate into the human genome but exists as stable episomal DNA that instructs the host cells to synthesise and secrete VRC07. Patients received a single injection and were monitored for a study period between 1-5 years and 3 years. No serious adverse events were attributed to the product during treatment or follow-up. Some patients’ serum was found to contain VRC07 after treatment, and this production remained stable for over a year after initial infection. Purified serum samples containing VRC07 were able to neutralise HIV in vitro, and the efficacy of neutralisation positively correlated with the measured VRC07 concentration. Not all patients responded equally to AAV8 treatment: three patients produced anti-VRC07 antibodies, which prevented the efficient production of the bNab. This study is the first reported case of in-human production of bNabs, and future work will focus on overcoming these anti-VRC07 antibodies.

4. Checkpoint paralysis

The body’s natural producer of antibodies, the immune system, is hampered by HIV infection. In people with HIV, immune checkpoint proteins (ie, proteins that inhibit immune system activation) are overexpressed, leading to T-cell exhaustion (even in patients on ART). Exhaustion is a dysfunctional state that is distinct from both functional memory and effector T cells and prevents the control of future infection and tumours. Chris Chiu (University of Melbourne, Melbourne, VIC, Australia) presented data from their study detailing efforts to remove immune checkpoint inhibition in people with HIV. Chiu and colleagues first obtained peripheral blood mononuclear cells (PBMCs) from 11 people with HIV and then stimulated them with two HIV peptides (Gag and Nef). Stimulation, with either Gag or Nef, resulted in production of IFNγ and TNFα from PBMCs. The cells
were then treated with antibodies able to bind and inhibit the activity of six immune checkpoint molecules (ie, CTLA-4, PD-1, PD-L1, TIM-3, TIGIT, and LAG-3). Antibodies were given singularly, in dual combinations or a cocktail of all six. PD-1 inhibition alone increased IFN\(\gamma\) and TNF\(\alpha\) expression in gag-stimulated CD4+ cells. Anti-LAG-3 combined with anti-TIGIT or with anti-CTLA-4 resulted in an increase in the number of gag-stimulated cells producing CD107a (a marker for degranulation in immune cells). Combinations of CTLA-4, TIGIT, TIM-3, PD-L1, and LAG-3 resulted in increased numbers of HIV-specific CD4+ and CD8+ cells expressing IL-2. TIGIT, an immune cell receptor present on T cells and natural killer (NK) cells, was the focus of work presented by Oscar Blanch-Lombarte (IrsiCaixa Institute for AIDS Research, Badalona, Spain). The group isolated PBMCs in chronically and longitudinal HIV-treated, patients who were in the early stages of HIV infection and healthy individuals and analysed the expression of inhibitory receptors (including TIGIT). Their data showed that memory CD8+ cells expressing TIGIT negatively correlated with the number of CD4+ cells counts. Single-cell cluster analysis showed wide inhibitor receptor heterogeneity. Analysis of HIV-specific CD8+ T cells identified a depletion of TIGIT\textsuperscript{high} memory-like clusters with loss of CD107a production in patients on long-term ART. However, short-term TIGIT antibody blockade in vitro restored the production of CD107a. Combined, these results point to the potential therapeutic potential of TIGIT for the treatment of people with HIV.

Opeyemi Adeniji (Wistar Institute, PA, USA) presented work on another inhibitory receptor, Siglec-9, which is expressed on a subset of cytolytic NK cells. Siglec-9 inhibits NK cell functions by binding to sialic acid found on the surface of target cells and has been implicated as a mechanism for tumour cells to evade the immune system. Adeniji and colleagues measured the frequency of Siglec-9 positive NK cells from three groups of participants: patients who are HIV negative, patients who are HIV positive with viremia, and patients who are HIV positive and on suppressive ART. The cytotoxicity of NK cells (with different Siglec-9 expression profiles) was also assessed in vitro. Their study found that Siglec-9+ NK cell frequency decreased during HIV infection and remained decreased despite ART. In vitro, NK cells expressing Siglec-9 produced more CD107a and IFN-\(\gamma\) and exhibited higher levels of cytotoxicity towards HIV+ cells compared with NK cells without or with depleted Siglec-9. Finally, inhibition of Siglec-9 by an antibody resulted in further enhanced HIV positive cell killing activity of NK cells that expressed Siglec-9. Inhibition of Siglec-9 and the activation of this subset of NK cells could represent potential therapeutic targets to enhance the ability of the immune system to target and kill HIV-infected cells during ART.

**Declaration of Competing Interest**

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests.