Note. ACCORD II no longer running at UHB.

RECOVERY

1. Lopinavir/ritonavir
    a. HIV type 1 (HIV-1) protease inhibitor (Cvetkovic & Goa) with activity on CYP proteins. Inhibits the action of 3CL enzyme which processes viral RNAto prevent viral replication within the cell.
    b. Potential MOA in SARS-CoV-2 by binding "3-chymotrypsin-like protease (3CLpro) as this plays a crucial role in processing the viral RNA (Dorward and Gbinigie)
2. Dexamethasone - corticosteroid limits inflammation to prevent severe tissue damage. Binds to glucocorticoid receptor to suppress inflammatory gene transcription and inactivate NFKB mediated proinflammatory gene transcription (reduce IL-1B, TNFa, IL-12, TFNg, IL-6 and IL-8, and IL-10 Newton
3. Hydroxychloroquine
    a. Exact MOA largely unknown. "Antimalarial drugs have direct molecular effects on lysosomal activity, autophagy and signalling pathways (Fig. 3). Data on the effects of these drugs on plasmacytoid dendritic cells (pDCs), B cells, other antigen-presenting cells and T cells are also available (Fig. 4)." (Schrezenmeier and Dörner)
    b. Disrupt lysosomes, impair antigen presentation (Schrezenmeier and Dörner)
    c. Inhibit palmitoyl-protein thioesterase 1 (PPT1) (Schrezenmeier and Dörner)
    d. Disrupt TLR7/9 signalling (Schrezenmeier and Dörner)
4. Tocilizumab
    a. Monoclonal antibody against IL-6 receptor - binds receptors preventing IL-6 from binding and exerting proinflammatory effects. IL-6 stimulates antibody production by b cells, T cell development, neutrophil recruitment etc - high levels lead to excess inflammation and ARDS
    b. Blocking IL-6 may calm the inflammatory storm and lessen lung damage in severe covid Fu
5. Azithromycin - macrolide antibiotic that also has anti-inflammatory properties and antiviral effects Gielen
    a. Inhibit IL-6 and IL-8 release to reduce neutrophil recruitment
    b. Increase IFN release in bronchial epithelial cells

SNG-001

- Interferon B1a
- Released by pDC on recognition of a virus by TLR. IFN binds to receptors on cells to activate gene transcription of inflammatory genes including antiviral mediators. These include enzymes that mediate viral RNA degradation, and those that activate apoptosis in virus infected cells. IFNs also promote DC maturation to facilitate CD4+ and CD8+ T cell differentiation.
- IFNb leads to a positive feedback loop that stimulates the expression of IFNa genes
- IFNb levels were low in high risk groups, including elderly - adding IFNb directly to the lungs may improve immune defences

- Refs - Sallard, Lin

REMAP-CAP

1. Dexamethasone
    a. corticosteroid limits inflammation to prevent severe tissue damage. Binds to glucocorticoid receptor to suppress inflammatory gene transcription and inactivate NFKB mediated proinflammatory gene transcription (reduce IL-1B, TNFa, IL-12, TFNg, IL-6 and IL-8, and IL-10 Newton
2. Hydroxychloroquine (HCQ)
    a. Exact MOA largely unknown. “Antimalarial drugs have direct molecular effects on lysosomal activity, autophagy and signalling pathways (Fig. 3). Data on the effects of these drugs on plasmacytoid dendritic cells (pDCs), B cells, other antigen-presenting cells and T cells are also available (Fig. 4).” (Schrezenmeier and Dörner)
    b. Disrupt lysosomes, impair antigen presentation (Schrezenmeier and Dörner)
    c. Inhibit palmitoyl-protein thioesterase 1 (PPT1) (Schrezenmeier and Dörner)
    d. Disrupt TLR7/9 signalling (Schrezenmeier and Dörner)
3. Lopinavir/ritonavir + HCQ
    a. Lopinavir and rionavir are protease inhibitors which together are licensed for the treatment of HIV (Yu).
    b. Lopinavir inhibits HIV protease enzyme formation (https://www.drugbank.ca/drugs/DB01601) and has modest activity in vitro against SARS-Cov (chen)
    c. Ritonavir inhibits CYP3 mediated metabolism of lopinavir which is why it is given in combination, and together they show effectiveness against SARS-CoV.
    d. Lopinavir/ritonavir significantly reduced the adverse outcomes (ARDS or death) in SARS patients (2.4% vs 28.8% p<0.001) Chu
4. Interferon B1a
    a. Interferon beta-a1 is a cytokine that helps to activate the body’s antiviral response
    b. Has been shown to reduce viral load of MERS (hung)
    c. Broad in vitro antiviral activity with modest in vitro activity against SARS-Cov (Chen)
5. Interleukin 1R antagonist
    a. Blocks activity of IL-1alpha and beta - will reduce high levels released by macrophages and immune cells in COVID Cavalli

Alxn1210-cov-305 (catchy name)

- Ravulizumab
    - Complement C5 inhibitor
    - Monoclonal antibody that binds to alpha chain of C5, preventing cleavage into C5a and C5b to inhibit the formation of membrane attack complex which punches holes in cell membrane to destroy cells. C5a also triggers inflammation, is chemotactic Horiuchi

- Previous study in mice shows C3 complement activation exacerbates SARS-COV mediated inflammation and ARDS (Gralinski et al., 2018,) review in Risitano et al
- C3 and C5 are closely involved in complement mediated activation of inflammation (Risitano et al., 2020)
- High serum C5a and C3 activation observed in severe COVID, with anti C5a antibody showing clinical promise (Gao et al., 2020) review in Risitano et al

CATALYST trial

- Gemtuzumab Ozogamicin
  - anti-CD33.
  - Monoclonal antibody known to bind CD33 expressing tumour cells
  - The antibody is covalently linked to a derivative of calicheamicin, a known antitumor agent. Drug binds to CD33, internalised and releases calicheamicin derivative to kill tumour cells by targeting DNA replication (Hitzler and Estey, 2019). Currently indicated for use in acute myeloid leukemia (AML) (BNF)
  - No information on NIHR on what aspect of COVID this trial is looking at. Also can't find on clinical trials gov. Mechanism suggests trial is designed for people with AML who get COVID or to target viral replication in cells?
- Namilumab
  - Targets GM-CSF
  - Targeting GM-CSF is aimed at inflammation driven by proliferation of myeloid cells such as inflammatory monocytes, macrophages, neutrophils (Taylor et al., 2019), which may help dampen the viral driven inflammation

ACCORD II

1. Bemcetinib
   a. Intracellular inhibitor of AXL receptor tyrosine kinase
   b. Has antiviral activity - inhibit AXL blocks virus entry and enhancing IFN response (ref) - showed promise in EBOLA and ZIKA
2. MEDI3056
   a. IL-33 inhibitor - IL-33 is produced by structural cells including epithelial and fibroblasts, and may function as an alarmin by dead cells. Chemoattractant to T cells and activates T cell function, activates macrophages Chan
   b. Inhibition may limit inflammatory response in the lung
3. Acalabrutinib
   a. Inhibitor of Brutans Tyrosine kinase (BTK)
   b. Involved in cytokine production in macrophages - IL-6, IL-10, TNFa, MCP-1 - so inhibition reduces levels of cytokines and reduce exaggerated inflammatory response in ARDS AZ
4. Zilucoplan
   a. Peptide inhibitor of complement C5
   b. C5 mechanism reviewed in Ravulizumab above

ILIAD-7

- Recombinant IL-7
    - Targets B Cells and T Cells proliferation, differentiation and maturation
    - IL-7 binds to receptors IL-7rα and common gamma chain to stimulate the JAK-STAT pathway leading to downstream PI3k, src and bcl-2 kinase activation and subsequent cell proliferation, differentiation and survival (Nguyen et al., 2017; Mackall et al., 2011)
    - Lymphopenia is prominent in severe COVID. Recombinant IL-7 (CYT 107) has been shown to increase absolute CD4+ and CD8+ T cells in septic patients with severe lymphopenia (Francois et al., 2018). It also increased absolute neutrophils with no significant difference in patient mortality
    - IL-7 administration downregulates IL-7rα expression (Francois et al., 2018), suggesting it acts through a feedback loop

GSK2193874

- TRPV4 antagonist
- TRPV4 is expressed on vascular endothelium in lung and regulates integrity of the alveolar septal barrier - allowing liquid into the lungs. Blocking this will reduce pulmonary edema Cheung

Missing Targets

- **ACE2 Inhibitors - for early covid**