COVID-19: Questions and Discussions. What about Answers?

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Topics for Discussion

- COVID-19 Epidemiology and Spread
- Vaccines
- COVID-19 and CLL
COVID-19 Cases

• As of April 10, 2021:

<table>
<thead>
<tr>
<th>Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>31,877,000</td>
</tr>
<tr>
<td>Worldwide</td>
<td>136,4290,000</td>
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</tbody>
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• In the US:
  – Achieved a third peak on January 8, 2021
  – Possible new peak versus plateau
Daily New Cases
(worldometers.com/coronavirus accessed 04/10/2021)
COVID-19 Variants

- B.1.1.7: UK
- B.1.351: South Africa
- B.1.427: California
- B.1.429: California
- P.1: Brazil

- New mutations develop constantly. Ones with advantages increase in incidence.
- Advantages typically in spread, not lethality
- MERS vs COVID-19
COVID-19 Spread Through a Room
Within a short time, the room approaches its peak level of contamination. With little fresh air coming into the space, the contaminants continue to circulate throughout the room.
Rapid COVID-19 Test

Diagram showing the interaction of RBCs with VHH(IH4) anti Glycophorin A and SARS-2 RBD. The outcomes are differentiated by the presence or absence of antibodies. No antibodies result in no agglutination, while the presence of antibodies leads to agglutination.
COVID-19 Virus
Vaccines

Vaccine Types:
RNA: Pfizer/BioNTech, Moderna
Non-replicating vector viruses:
  AstraZeneca/Oxford (ChAdOx1)
  J and J (Ad26COVS1)
Protein-based: Novavax (NVX-CoV2373)
How the J and J Vaccine Works

CORONAVIRUS

Spikes

Spike protein gene

VACCINATED CELL

Entering the cell

Leaving the bubble

Viruses expelled in a bubble

Injecting DNA

DNA → mRNA → mRNA

CELL NUCLEUS
How mRNA Vaccines Work
Pfizer Vaccine Efficacy

• Israeli Study (not approval study) demonstrated:
  – 93.7% reduction in symptomatic COVID-19 cases
  – 89.4% reduction in asymptomatic COVID-19 cases
Efficacy of AZ Vaccine post-Dose 1 vs 2

Vaccine Efficacy (AstraZeneca)

• Endpoint: NAAT-confirmed, symptomatic infection (nucleic acid amplification test=PCR)

• Symptomatic COVID-19 infections in:
  • vaccinated: 30 out of 5807 (0.5%)
  • placebo: 101 out of 5829 (1.7%)
  • vaccine efficacy in reducing symptomatic infection = 70.4%

• Positive COVID-19 nasal swabs in asymptomatic individuals:
  • vaccinated: 1.2%
  • placebo: 2.6%
  • vaccine efficacy in reduction of asymptomatic infections = 55.7%
Vaccine Efficacy Against Variants

• B.1.351: Janssen=57%, Novavax=49%, AZ: not effective
COVID-19 in Patients with CLL

• Data indicates immune system important in causing complications
  – cytokine storm, complement activation
• Factors impacting COVID-19 in CLL patients:
  1. Immune dysfunction
     • Immune dysfunction: protective vs harmful?
     • T vs B cell dysfunction?
     • no COVID-19 immunity in IV IG
  2. Advance age
  3. Morbidity due to interruption of therapy
COVID-19 in CLL - Mato

• Multicenter, international cohort study of patients with symptomatic COVID-19 infection
• Patients (N=198) with CLL and symptomatic COVID-19 confirmed by RNA
• Characteristics:
  – median age = 70.5 years
  – median CIRS score = 8
  – TN (watch and wait) = 39%
  – Receiving active treatment = 45%
    • BTKi = 76%
• median follow up 16 days (25% of pts remain admitted)
COVID-19 in CLL - Results

- case fatality rate: 33% (25% of pts remain admitted)
  - 50% in those discharged
- No difference in outcomes for watch-and-wait versus treated patients

<table>
<thead>
<tr>
<th></th>
<th>WW</th>
<th>Tx</th>
</tr>
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<tbody>
<tr>
<td>Admission rate</td>
<td>89%</td>
<td>90%</td>
</tr>
<tr>
<td>ICU admission</td>
<td>35%</td>
<td>36%</td>
</tr>
<tr>
<td>Intubation</td>
<td>33%</td>
<td>25%</td>
</tr>
<tr>
<td>Mortality</td>
<td>37%</td>
<td>32%</td>
</tr>
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</table>

- BTKi therapy did not impact survival: 34% vs 35%
  - BTKi therapy held during COVID-19 admission for 79% of patients
  - in 14 patients who remained on BTKi, case fatality rate: 21%

Mato AR. Blood 2020; 136:1134
COVID-19 in CLL: Summary

- only examined symptomatic patients
- bias in those tested
- no age match comparator
- possible protective effect of BTKi therapy (not statistically confirmed)
## COVID-19 Therapeutics

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Intervention</th>
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<tbody>
<tr>
<td>viral replication</td>
<td>remdesivir, bamlanivimab, casirivimab + imdevimab, convalescent plasma</td>
</tr>
<tr>
<td>complement activation</td>
<td>eculizumab, ravulizumab</td>
</tr>
<tr>
<td>coagulopathy</td>
<td>anticoagulation</td>
</tr>
<tr>
<td>cytokine storm: IL-1, IL-6, GM-CSF</td>
<td>dexamethasone, anakinra (IL-1), sarilumab/tocilizumab (IL-6), mavrilimumab (GM-CSF), BTK inhibitors, fluvoxamine</td>
</tr>
</tbody>
</table>

- Sarilumab trial halted; tocilizumab not beneficial in survival
BTK Inhibitors in COVID-19

- BTK inhibition rescues mice from lethal influenza-A infection
  - see decrease in macrophage cytokines: TNF$\alpha$, IL-1, IL-6
- BTK inhibition results in decreases in TNF$\alpha$, IL-10, MCP-1, MIP-1, IL-6 in humans
- NIH (severe COVID-19): 19 pts: 11 supplemental O2 (0 deaths), 8 intubated (2 deaths)
- Large, phase 3 studies on-going
  - CALAVI (acalabrutinib) study negative
    - Looked at hospitalized patients with respiratory symptoms
    - Endpoints: alive and free of respiratory failure
My Approach:

• delay initiation of treatment (no longer applicable)
• for patients requiring therapy: BTK inhibitors therapy of choice
  – does not require aggressive monitoring
  – no infusion center appointments
  – possible protective effect
• for patients on therapy when infected with COVID-19:
  – continue BTK inhibitor
  – hold others: PI3K inhibitor (?)
• supportive care as per institutional guidelines: anticoagulation