The Management of Immunocompromised Patients During COVID-19

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Disclosures

• Consulting: Viela Bio/Horizon, MedPace, Sanofi/Principia, Zenas Biopharma

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• Advisory Board: Sanofi/Principia
Objectives

• Review data on the risk of COVID-19 and outcomes of COVID-19 among patients with immune-mediated disease treated with immunomodulators

• Discuss the effects of immunomodulation on the immune response to COVID-19 vaccination and vaccine efficacy

• Consider risk mitigation strategies for immunosuppressed patients during the COVID-19 pandemic
Association of Immune-Mediated Inflammatory Diseases with COVID-19

• Recent meta-analysis suggested that systemic rheumatic diseases had an increased risk of COVID-19 infection (HR 1.5, 95% CI 1.2-2.0)
• Early data from UK OpenSAFELY indicated that RA, SLE, and psoriasis was associated with an increased risk of COVID-19 death
• This is a diverse population of patients
• Risk factors for worse COVID-19 outcomes in immune-mediated diseases (e.g., rheum, psoriasis, IBD) include:
  • Age, sex, race, comorbidities
  • Worse disease control / glucocorticoid use
  • Certain immunomodulator treatments

Conway, et al Arthritis Rheum 2022 (Epub); Nature 2020; 584:430
Demographics and Comorbidities Associated with Hospitalization

### Rheumatic Disease (n=600)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>0.83 (0.54,1.28)</td>
<td>0.39</td>
</tr>
<tr>
<td>Age</td>
<td>2.56 (1.62, 4.04)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

**Common diagnoses:**
- RA
- SLE
- SpA -PsA
- SpA – AS or other
- Vasculitis
- Other

**Common comorbidities**
- HTN or CVD
- Lung Disease
- Diabetes
- CKD/ESRD

### Psoriasis (n=374)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>2.51 (1.23-5.12)</td>
</tr>
<tr>
<td>Age (/10 years)</td>
<td>1.59 (1.19-2.13)</td>
</tr>
<tr>
<td>Non-White Ethnicity</td>
<td>3.15 (1.24-8.03)</td>
</tr>
<tr>
<td>Ever Smoked</td>
<td>1.16 (0.54-2.49)</td>
</tr>
</tbody>
</table>

**Comorbidities**
- Lung Disease
- Hypertension
- CVD

Ann Rheum Dis 2020;79:859; JACI 2021;147:60
# Racial Disparities in COVID-19 in Patients with Rheumatic Diseases in the USA

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Hospitalization N=599</th>
<th>Ventilation N=540</th>
<th>Death N=681</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Black</td>
<td>2.70 (1.66, 4.42)</td>
<td>3.10 (1.77, 5.41)</td>
<td>1.10 (0.49, 2.50)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1.98 (1.17, 3.33)</td>
<td>2.97 (1.63, 5.41)</td>
<td>1.78 (0.84, 3.78)</td>
</tr>
<tr>
<td>Other/Mixed Race</td>
<td>1.79 (0.93, 3.44)</td>
<td>2.34 (1.11, 4.95)</td>
<td>1.22 (0.35, 4.26)</td>
</tr>
</tbody>
</table>

Estimates are OR (95% CI)

Arthritis Rheum 2021;73:374
Immunomodulator Use and Risk of COVID-19: Exposure Timing

- Dexamethasone
- JAK inhibitors
- IL-6 inhibitors

Disease Severity

- Viral response
- Host response

Stage I
- (early infection)
- Lymphocytopenia
- ~5 days

Stage II
- (pulmonary phase)
- Abnormal chest imaging
- ~10 days

Stage III
- (hyperinflammation)
- Elevated inflammatory and cardiac biomarkers

Time Course (days after symptoms appear)
Early Data from the Global Rheumatology Alliance: Associations with Hospitalization

• The first 600 patients with rheumatic disease enrolled in the physician-reported registry early in the pandemic
• Age and comorbidity burden associated with COVID-19 hospitalization
• Varied odds of hospitalization across DMARD categories
• Potential protective benefit of TNFi use

<table>
<thead>
<tr>
<th>DMARD Category</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No DMARD (Ref)</td>
<td>1.0</td>
</tr>
<tr>
<td>csDMARD only</td>
<td>1.2 (0.7-2.2)</td>
</tr>
<tr>
<td>b/tsDMARD only</td>
<td>0.5 (0.2-0.9)</td>
</tr>
<tr>
<td>TNFi use</td>
<td>0.4 (0.2-0.8)</td>
</tr>
<tr>
<td>csDMARD &amp; b/tsDMARD</td>
<td>0.7 (0.4-1.5)</td>
</tr>
</tbody>
</table>
Association of TNFi with risk of hospitalization or death across IMIDs

- Pooled analysis across three large registries
- 6,077 patients with rheumatic disease, psoriasis, and inflammatory bowel disease
- TNF inhibitor monotherapy was associated with lower odds of hospitalization or death compared with:
  - TNFi + 6MP/AZA
  - MTX monotherapy
  - JAKi monotherapy
Early Data from the Global Rheumatology Alliance: Associations with Death

- Extended follow up of GRA registry (through July 1, 2020)
- N=3,729
- Medications associated w/ death:
  - Rituximab (OR 4.0)
  - Sulfasalazine (OR 3.6)
  - AZA/CYC/MMF/Tacro (OR 2.2)
- Trends:
  - JAKi → higher risk?
  - IL-6i → lower risk?
  - Steroids → higher risk?

Ann Rheum Dis 2021;80:930
Differential Effects of TNFi and SSZ

**TNF inhibition**
- B→T
- Tfh
- Bcl-6+ Tfh
- Follicle with Germinal Centers

**Sulfasalazine**
- Viral or self nucleic acids
- TLR9
- SARS-CoV-2
- pDC
- Type I IFN
- Sulfasalazine
- Inhibition of type I IFN
- Might ameliorate
- Autoimmunity
- SLE
- Sjögren’s syndrome
- DM/CADM
- Interferonopathies
- Aicardi-Goutières syndrome
- CANDLE
- SAVI

Other Immunogens:
- OTHER IMMUNOGENS
- SARS-COV-2
- B→T
- Th1
- TNF alpha secreting cells
- No Germinal centers

Protective antiviral immunity

Cell 2020;183:143
Lancet Rheumatol 2022 (Konig et al)
Association of b/tsDMARDs with Severe COVID-19 in RA: Data from the GRA

<table>
<thead>
<tr>
<th>Drug</th>
<th>Multivariable*</th>
<th>PS-matched†</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABA</td>
<td>1.26 (0.88, 1.80)</td>
<td>1.60 (1.02, 2.51)</td>
</tr>
<tr>
<td>RTX</td>
<td>4.15 (3.16, 5.44)</td>
<td>4.70 (3.31, 6.65)</td>
</tr>
<tr>
<td>IL-6i</td>
<td>0.81 (0.56, 1.18)</td>
<td>0.76 (0.46, 1.23)</td>
</tr>
<tr>
<td>JAKi</td>
<td>2.06 (1.60, 2.65)</td>
<td>2.09 (1.50, 2.90)</td>
</tr>
</tbody>
</table>

Reference: TNFi
The Impact of B Cell Depletion on COVID-19 Outcomes

- Compared to general population, B cell depletion (for non-oncology indications) was associated with higher risk of death (HR 2.2, 95% CI 1.03-4.5)
- Among B cell depleted patients, more recent B cell depletion treatment may be associated with more severe COVID-19
- These patients may be at high risk for prolonged hospital course and re-infection (17% in one study)
Within Host Viral Evolution

Within-host evolution of SARS-CoV-2 in an immunosuppressed COVID-19 patient as a source of immune escape variants

Case Study: Prolonged Infectious SARS-CoV-2 Shedding from an Asymptomatic Immunocompromised Individual with Cancer
Part 1 Summary

• In general, immune-mediated diseases are associated with a higher risk of COVID-19 but this is a diverse population and risks will vary among individuals

• Similar risk factors for severe disease as in the general population

• Certain immunomodulators likely predispose to more severe disease
  • B cell depletion
  • Conventional DMARDs (e.g., Mycophenolate, Azathioprine, Calcineurin Inhibitors)
  • Sulfasalazine
  • JAK inhibitors

• Other immunomodulators may **not** be associated with more severe disease (and be protective?)
  • TNF inhibitors
  • IL-6 inhibitors
Vaccination of Immunosuppressed Patients

• Vaccines are safe in patients who are immunosuppressed
  • In a large survey-based study (n=5,121 with rheumatic disease), < 5% of patients experienced a flare and, of these, < 1% were severe
  • Total and Serious AEs were similar in those with and without immunosuppressed conditions (Total: 37% vs 40%, Serious: 0.4% vs 1.9%)

• The immune response to vaccination may be blunted in immunosuppressed patients
  • Reduced quantity of antibody response
  • Reduced quality/function of antibody response (e.g., variant-specific neutralizing antibodies)
  • Faster waning of antibody response
  • Reduced T cell responses

Machado, et al Ann Rheum Dis 2021 (Epub)
Grainger, Nat Rev Rheumatol 2022 (Epub)
Blunted Antibody Responses

- Anti-metabolites
  - Methotrexate
  - Mycophenolate
  - Azathioprine
  - Tacrolimus
  - Cyclosporine
- B cell depleting agents
  - Rituximab
  - Ocrelizumab
  - Others
- Glucocorticoids
Immune Dysfunction and Breakthrough Infection: Retrospective US-based Study

Breakthrough infections after vaccination among rheumatic diseases

Cumulative incidence of COVID-19 post vaccine breakthrough infection, per 1000 persons

Risk of breakthrough COVID-19 infection

<table>
<thead>
<tr>
<th>Disease</th>
<th>OR (95% CI)</th>
<th>Drug</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>1.33 (1.20, 1.48)</td>
<td>nbDMARD</td>
<td>1.06 (0.89, 1.25)</td>
</tr>
<tr>
<td>SpA</td>
<td>1.00 (0.90, 1.12)</td>
<td>bDMARD</td>
<td>1.61 (1.18, 2.14)</td>
</tr>
<tr>
<td>Gout</td>
<td>1.14 (1.05, 1.24)</td>
<td>Prednisone</td>
<td>1.03 (0.98, 1.08)</td>
</tr>
<tr>
<td>SLE</td>
<td>1.04 (0.82, 1.31)</td>
<td>tsDMARD</td>
<td>0.72 (0.12, 2.28)</td>
</tr>
<tr>
<td>SSc</td>
<td>0.97 (0.61, 1.46)</td>
<td>Colchicine</td>
<td>1.02 (0.81, 1.27)</td>
</tr>
<tr>
<td>Polymyositis</td>
<td>1.97 (1.07, 3.33)</td>
<td>Urate lowering</td>
<td>1.11 (0.97, 1.26)</td>
</tr>
<tr>
<td>PMR</td>
<td>1.20 (0.93, 1.53)</td>
<td>Other IS meds</td>
<td>1.09 (0.92, 1.27)</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>1.19 (1.05, 1.33)</td>
<td>Multiple meds</td>
<td>1.38 (1.29, 1.48)</td>
</tr>
<tr>
<td>Multiple</td>
<td>1.17 (1.03, 1.31)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Vaccine Recommendations

• All patients with immunomodulation/immunosuppression should be vaccinated, regardless of disease activity

• Some data support the holding medications before/after vaccination to improve the response
  • For B cell depleting agents, vaccination should be timed to occur prior to next treatment and prolonged until B cell repopulation, if possible

• mRNA recommended over J&J vaccination

• Immunosuppressed patient vaccination:
  • Primary Series: 3 mRNA vaccines or 1 J&J + mRNA vaccine
  • Booster: 4th dose, as soon as 3 months after most recent mRNA vaccine (or 3rd dose for people who received J&J first)

• Unclear role of spike antibody testing to assess response to vaccination
<table>
<thead>
<tr>
<th>Medication</th>
<th>Timing Considerations for Immunomodulatory Therapy and Vaccination</th>
<th>Level of Task Force Consensus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abatacept IV</td>
<td>Time vaccination so that it occurs one week prior to the next dose of IV abatacept</td>
<td>Moderate</td>
</tr>
<tr>
<td>Abatacept SQ</td>
<td>Hold for one to two weeks (as disease activity allows) after each COVID vaccine dose</td>
<td>Moderate</td>
</tr>
<tr>
<td>Acetaminophen, NSAIDs</td>
<td>Assuming that disease is stable, hold for 24 hours prior to vaccination. No restrictions on use post vaccination once symptoms develop.</td>
<td>Moderate</td>
</tr>
<tr>
<td>Belimumab SQ</td>
<td>Hold for one to two weeks (as disease activity allows) after each COVID vaccine dose</td>
<td>Moderate</td>
</tr>
<tr>
<td>TNFI, IL-6R, IL-1R, IL-17, IL12/23, IL-23, and other cytokine inhibitors†</td>
<td>The Task Force failed to reach consensus on whether or not to temporarily interrupt these following each COVID vaccine dose, including both primary vaccination and supplemental (booster) dosing</td>
<td>Moderate</td>
</tr>
<tr>
<td>Cyclophosphamide IV</td>
<td>Time CYC administration so that it will occur approximately 1 week after each vaccine dose, when feasible</td>
<td>Moderate</td>
</tr>
<tr>
<td>Hydroxychloroquine, IVIG</td>
<td>No modifications to either immunomodulatory therapy or vaccination timing</td>
<td>Strong (HCQ), Moderate (IVIG)</td>
</tr>
<tr>
<td>Rituximab or other anti-CD20 B-cell depleting agents</td>
<td>Discuss the optimal timing of dosing and vaccination with the rheumatology provider before proceeding‡</td>
<td>Moderate</td>
</tr>
<tr>
<td>All other conventional and targeted immunomodulatory or immunosuppressive medications (e.g., JAKi, MMF) except those listed above§</td>
<td>Hold for one to two weeks (as disease activity allows) after each COVID vaccine dose</td>
<td>Moderate</td>
</tr>
</tbody>
</table>
Managing COVID-19 Risk and Infection

Risk Mitigation

Post-Acute Sequelae of COVID-19 (PASC) or “Long-Haul” COVID

Adjuvantive therapies
Anticoagulants
NSAIDs etc.

Recovery (~80%)

Healthy

Recovery (~80%)

Mild to moderate (~60%)

Replication inhibitors
Remdesivir
Molnupiravir
Paxlovid

Neutralizing monoclonal antibodies
Bamlanivimab plus etesevimab
Casirivimab plus imdevimab
Sotrovimab
Tixagevimab plus cilgavimab
Regdanvir
Amubarvimab plus romlusevimab

Immunomodulatory therapies
Dexamethasone
Baricitinib or tofacitinib
Tocilizumab or sarilumab
Risk Mitigation Strategies

• Vaccination will be effective for many patients using immunomodulatory therapy but the efficacy is likely blunted compared to non-immunosuppressed patients
  • Booster doses are critical in this population
  • Encourage family members to also be vaccinated

• Masking and social distancing is important for patients with severe immunosuppression who are unlikely to respond to vaccination

• Early testing strategies (home rapid tests, PCR tests) and making a plan of who to contact in the event of infection are important

• Pre- and post-exposure prophylaxis may be a game-changer for immunocompromised population during COVID-19

• If infected, access to early treatment is critical
Pre- and Post-Exposure Prophylaxis

• This is a moving target because of viral evolution and resistance to treatments associated with delta and omicron variants

• The only options for prophylaxis are monoclonal antibodies but there may be a future role for oral antivirals (e.g., paxlovid)

• Evusheld (tixageviman/cilgavimab) is the only FDA-authorized monoclonal for use as pre-exposure prophylaxis (supplies remain very limited)
  • The FDA recently indicated that to retain efficacy against Omicron, patients need to receive two doses

• Two monoclonal antibodies currently available with efficacy against Omicron but neither approved for post-exposure prophylaxis
  • Sotrovimab and Bebtelovimab

• This is a rapidly evolving space and we expect that new options will continue to become available in the near future
# Early Treatment Options for COVID-19

<table>
<thead>
<tr>
<th>Therapeutic</th>
<th>Mode of Action</th>
<th>Reduction in Hospitalization</th>
<th>Boxed = retained efficacy against Omicron variants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remdesivir</td>
<td>Nucleotide Analog</td>
<td>87%</td>
<td>retains efficacy against Omicron variants</td>
</tr>
<tr>
<td>Monupiravir</td>
<td>Nucleotide Analog</td>
<td>30%</td>
<td>retains efficacy against Omicron variants</td>
</tr>
<tr>
<td>Paxlovid</td>
<td>Protease Inhibitor</td>
<td>90%</td>
<td>retains efficacy against Omicron variants</td>
</tr>
<tr>
<td>Bamlanivimab and etesevimab</td>
<td>mAb</td>
<td>70%</td>
<td>not in use</td>
</tr>
<tr>
<td>Casirivimab and imdevimab</td>
<td>mAb</td>
<td>66%</td>
<td>not in use</td>
</tr>
<tr>
<td>Sotrovimab</td>
<td>mAb</td>
<td>85%</td>
<td>retains efficacy against Omicron variants</td>
</tr>
<tr>
<td>Tixagevimab and cilgavimab</td>
<td>mAb</td>
<td>77%</td>
<td>pre-exposure prophylaxis</td>
</tr>
<tr>
<td>Regdanvimab</td>
<td>mAb</td>
<td>70%</td>
<td>not in use</td>
</tr>
<tr>
<td>Amubarvivmab and romlusevimab</td>
<td>mAb</td>
<td>80%</td>
<td>not in use</td>
</tr>
<tr>
<td>Bebtelovimab</td>
<td>mAb</td>
<td>Not Available</td>
<td>retains efficacy against Omicron variants</td>
</tr>
</tbody>
</table>

mAbs may also be considered as post-exposure prophylaxis depending on availability/approval.
Early Treatment of COVID-19

• Hold immunosuppression for 7-14 days after symptom onset or 10-17 days after a positive test

• Paxlovid, molnupiravir, and remdesivir have retained efficacy against current SARS-CoV-2 variants
  • Paxlovid >>> efficacy than molnupiravir and preferred per NIH
  • Paxlovid has a number of drug interactions which need to be carefully assessed before prescribing and dose-adjusted with CKD
  • Outpatient remdesivir is three days of IV infusion (caution in CKD, GFR > 30)

• Combination therapy may be necessary in severely immunosuppressed but not well-studied
## Paxlovid Drug Interactions

### Category B — Potential interaction but may be manageable

<table>
<thead>
<tr>
<th>Category</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Statins</strong> — hold 8 days, pitavastatin and pravastatin do not need to be held</td>
<td>DOACs — dabigatran and edoxaban likely safe, apixaban seek expert advice, avoid rivaroxaban</td>
</tr>
<tr>
<td><strong>Alpha-1 blockers</strong> — hold tamsulosin and others for 8 days</td>
<td>Warfarin — monitor, INR may fall out of therapeutic range</td>
</tr>
<tr>
<td><strong>Inhaled beta agonists</strong> — hold salmeterol for 8 days, formoterol/albuterol fine</td>
<td>Calcineurin inhibitors — Avoid if possible, careful monitoring and dose adjustment</td>
</tr>
<tr>
<td><strong>Calcium channel blockers</strong> — may increase CCB concentration, monitor or dose reduce</td>
<td>Antipsychotics — Many in Category C, avoid if possible, dose reduction needed</td>
</tr>
<tr>
<td><strong>Opiates</strong> — consider dose decrease by 50-75% for 8 days, except methadone</td>
<td>Oral contraceptives — Barrier method recommended until next cycle</td>
</tr>
<tr>
<td><strong>Oral corticosteroids</strong> — monitor, consider 50-75% dose reduction</td>
<td>Triptans — hold eletriptan, sumatriptan fine</td>
</tr>
<tr>
<td><strong>Sildenafil/tadalafil/vardenafil</strong> — hold for 8 days</td>
<td>Chemotherapy and small molecule inhibitors — review with oncology</td>
</tr>
</tbody>
</table>
# Paxlovid Drug Interactions

## Category C — Nirmatrelvir-ritonavir should not be used

<table>
<thead>
<tr>
<th>Amiodarone</th>
<th>Eplerenone</th>
<th>Pimozone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apalutamide</td>
<td>Ergot derivatives</td>
<td>Propafenone</td>
</tr>
<tr>
<td>Bosentan</td>
<td>Flecaïnide</td>
<td>Quinidin</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Flibanserin</td>
<td>Ranolazine</td>
</tr>
<tr>
<td>Cisapride</td>
<td>Glecaprevir/pibrentasiv</td>
<td>Rifampin /Rifapentine</td>
</tr>
<tr>
<td>Clopidogrel (in high risk for thrombosis)</td>
<td>Ivabradine</td>
<td>Rivaroxaban</td>
</tr>
<tr>
<td>Clozapine</td>
<td>Lumateperone</td>
<td>Sildenafil (for pulmonary hypertension)</td>
</tr>
<tr>
<td>Colchicine (in hepatic/renal impairment)</td>
<td>Lurasidone</td>
<td>St. John’s wart</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>Mexiletine</td>
<td>Taladafil (for pulmonary hypertension)</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>Phenobarbital</td>
<td>Ticagrelor</td>
</tr>
<tr>
<td>Dronedarone</td>
<td>Phenytoin</td>
<td>Vorapaxar</td>
</tr>
</tbody>
</table>
Early Treatment with Monoclonal Antibodies

• This also continues to evolve quickly as new variants emerge that may be resistant to monoclonals

• Generally reserved for outpatients early in their disease course (within 7 days) but may be considered for hospitalized patients unlikely to mount a humoral response (e.g., B cell depleted)
  • Recent trial demonstrated efficacy limited to hospitalized patients without a serologic response to infection

• Only available options are Sotrovimab and Bebtelovimab (last resort option) because of preserved efficacy against Omicron
Conclusions

• Risks of COVID-19 outcomes vary across immunomodulators
• TNF inhibitors may be associated with lower risks of severe COVID-19
• JAK inhibitors and sulfasalazine may be associated with worse outcomes
• B cell depletion is associated with a higher risk of severe COVID-19 outcomes, including prolonged infection and within host evolution
• Vaccination is the most effective strategy to prevent COVID-19 and will be effective for the majority of our patients but some will have a blunted response and be at higher risk for breakthrough infection
• Pre-exposure prophylaxis is critical for high-risk immunosuppressed
• Access to early treatment can prevent progression to severe disease