Information on Clinical Trials Relevant to Uveitis

Systemic Corticosteroids

1. **Data on corticosteroids for COVID-19:**
    1. Most studies show negative effects of corticosteroids on similar viruses
        1. There is no clinical evidence of net benefit from steroids in SARS-CoV, MERS-CoV or influenza infection, and observational data show increased mortality, more secondary infections, impaired viral clearance and more adverse effects in survivors (*e.g.,* psychosis, diabetes, avascular necrosis) (Lee et al, *J Clin Virol*, 2004; Stockman et al, *PLoS Med*, 2006; Arabi et al, *Am J Respir Crit Care Med*, 2018; WHO, *COVID-19 Interim guidance*, March 2020; Wu et al, *JAMA Int Med*, 2020).
    2. However, a new retrospective cohort (201 patients, 84 [42%] of whom developed ARDS) demonstrated that among patients with ARDS, methylprednisolone decreased risk of death (HR, 0.38; 95% CI, 0.20-0.72) (Wu et al, *JAMA Int Med*, 2020).
2. **Recommendation**:
    1. **We recommend against using steroids for COVID-19 except as part of a clinical trial or if treating another indication**
        1. This is in line with WHO guidance (WHO, *COVID-19 Interim guidance*, March 2020).
    2. If required, use corticosteroids at the lowest dose for the shortest duration:
        1. Asthma or COPD exacerbation
            1. 40mg prednisone PO or 30mg methylprednisolone IV, once daily x 3-5 days
        2. Shock with history of chronic steroid use > 10mg prednisone daily:
            1. 50mg hydrocortisone IV Q6H until improvement in shock
        3. Multipressor shock without history of chronic steroid use
            1. 50mg hydrocortisone IV Q6H until improvement in shock

Anti-IL6 Agents (Tocilizumab, Siltuximab)

1. **Pathophysiology:**

    1. IL-6 activates T cells and macrophages, among other cell types (see "Cytokine Activation Syndrome" section in "Shock" chapter).

        1. IL-6 inhibitors are approved for cytokine activation syndrome complications related to Chimeric Antigen Receptor T cell (CAR-T) therapy (Brudno and Kochenderfer, *Blood Rev*, 2019; Rubin et al, *Brain*, 2019).
        2. IL-6 levels are reported to correlate with severe COVID-19
        3. While patients have peripheral lymphopenia, BAL fluid is often lymphocytic, suggesting that IL-6 inhibition and prevention of T cell activation may be protective.

2. **Recommendation:**

    1. We do not recommend routine use at this time

        1. There are anecdotal reports of benefit of tocilizumab in COVID-19 patients but no rigorous studies are available (Anecdotal reports from Italy; National Health Commission & State Administration of Traditional Chinese Medicine, *Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia [Trial Version 7]*, March 2020)

    2. For severe cytokine activation syndrome cases (see "Other Guidance" chapter):

        1. To be used in conjunction with Infectious Disease consultation in severe COVID-19 disease with suspicion of cytokine release syndrome (CRS).

            1. Retrospective reviews in patients with rheumatological disease suggested a possible increase in serious bacterial infection, so it may be reasonable to exercise caution if secondary infection is clinically suspected. However, tocilizumab is routinely used at BWH (*e.g.*, CRS in patients after CAR-T cell treatment) without obvious increase in bacterial infection.

3. **Dosing regimens:**

    1. Tocilizumab 4-8mg/kg (suggested dose 400mg) IV x1 (anti-IL6R mAb)

        1. Dose can be repeated 12h later if inadequate response to the first dose. Total dose should be no more than 800mg. Tocilizumab should not be administered more than twice.
        2. Common adverse effects include:

            1. Transaminitis (AST, ALT) > 22%
            2. Infusion reaction 4-20%
            3. Hypercholesterolemia 20%
            4. Upper respiratory tract infection 7%
            5. Neutropenia 2-7%

    2. Alternative: Siltuximab 11mg/kg IV x1 (anti-IL6 mAb)

        1. Common adverse effects include:

            1. Edema >26%
            2. Upper respiratory infection >26%
            3. Pruritus / skin rash 28%
            4. Hyperuricemia 11%
            5. Lower respiratory tract infection 8%
            6. Thrombocytopenia 8%
            7. Hypotension 4%

Hydroxychloroquine and Chloroquine

1. Pathophysiology:

1. Hydroxychloroquine (HQ) is an anti-malarial 4-aminoquinoline shown to have in vitro (but not yet in-vivo) activity against diverse RNA viruses including SARS-CoV-1 (Touret and de Lamballerie, Antivir Res, 2020).
2. HQ is thought to act through multiple mechanisms (Devaux et al, Int J Antimicrob Agent, 2020):

1. Inhibition of viral entry. HQ inhibits synthesis of sialic acids and interferes with protein glycosylation, which may disrupt interactions necessary for viral attachment and entry (Vincent et al, Virol J, 2005; Olofsson et al, Lancet Infect Dis, 2005).
2. Inhibition of viral release into the host cell. HQ blocks endosomal acidification, which activates endosomal proteases. These proteases are required to initiate coronavirus/endosome fusion that releases viral particles into the cell (Yang et al, J Virol 2004).
3. Reduction of viral infectivity. HQ has been shown to inhibit protein glycosylation and proteolytic maturation of viral proteins. Studies on other RNA viruses have shown a resulting accumulation of non-infective viral

particles, or an inability of viral particles to bud out of the host cell (Savarino et al, J Acquir Immune Defic Syndr, 2004; Klumperman et al, J Virol, 1994).
4. Immune modulation. HQ reduces toll-like receptors and cGAS-STING signaling. It has been shown to reduce release of a number of pro-inflammatory cytokines from several immune cell types (Schrezenmeier and Dorner, Nat Rev Rheum, 2020).

2. Data:

1. An expert consensus group out of China suggests that Chloroquine improved lung imaging and shortened disease course (Zhonghua et al, CMAPH, 2020). Chloroquine will be included in the next treatment guidelines from the National Health Commission, but the specific data on which this is based is not available yet (Gao et al, Biosci Trends, 2020).
2. Hydroxychloroquine was found to be more potent than chloroquine in inhibiting SARS-CoV-2 in vitro (Yao et al, Clin Infect Dis, 2020)

3. Recommendation:

1. Strong consideration of hydroxychloroquine in patients who require supplemental oxygen, or in those not on supplemental oxygen but at high risk for progression to severe disease, who are not candidates for other clinical trials.

4. Dosing (from published literature):

1. Hydroxychloroquine:

1. 400mg PO BID on the first day, followed by 200mg q12 (q8h if concerns for absorption) for 5-10 days

2. Chloroquine (not available at BWH and no plans to start use):

1. 500mg Chloroquine phosphate 500mg PO BID for 10 days
2. Increased toxicity compared to hydroxychloroquine with potential adverse effects including:

1. Prolonged QT interval and risk of Torsade de pointes
2. Cardiomyopathy
3. Bone marrow suppression
4. Contraindicated in epilepsy and porphyria

5. Monitoring

1. If hydroxychloroquine is being administered with azithromycin, there should be vigilant QTc monitoring:

1. Obtain baseline ECG and daily ECG
2. Discontinue all other QT prolonging agents
3. Maintain continuous telemetry while under treatment

4. Do not start if QTc >500 or 550 with pacing or BBB.
5. Discontinue if there is an increase in PVCs or non-sustained PMVT.

2. There is a reported risk of hydroxychloroquine induced cardiomyopathy. Case series and reports have found this to be a long-term (years) and dose-dependent phenomenon. Given the anticipated short duration in COVID-19, it is not an expected risk (Nord et al, Semin Arthritis Rheum, 2004).

Angiotensin Converting Enzyme Inhibitors (ACE-I) and Angiotensin II Receptor Blockers (ARB)

1. **Pathophysiology:**
    1. SARS-CoV-2, the virus that causes COVID-19, enters via the same cell entry receptor as SARS-CoV: angiotensin converting enzyme II (ACE2) (Paules et al, *JAMA*, 2020). SARS-CoV-2 is thought to have a higher affinity to ACE2 than SARS-CoV.
        1. ACE2 is expressed in the heart, lungs, vasculature, and kidneys. ACEi and ARBs in animal models increase the expression of ACE2 (Zheng et al, *Nat Rev Cardiol*, 2020), though this has not been confirmed in human studies. This has led to the hypothesis that ACE-I and ARBs, might worsen myocarditis or precipitate ACS.
        2. It has also been hypothesized that the upregulation of ACE2 is therapeutic in COVID-19 and that ARBs might be protective in during infection (Gurwitz D, *Drug Dev Res*, 2020).
2. **Recommendation:**
    1. For outpatients:
        1. We recommend against discontinuing outpatient ACEi/ARBs.
    2. For inpatients:
        1. We recommend against routine discontinuation of ACEi/ARBs, unless otherwise indicated (*e.g.,* acute kidney injury, hypotension, shock, etc).
    3. Rationale
        1. The American College of Cardiology, American Heart Association and Heart Failure Society of America joint statement recommends against discontinuing ACE-I and ARBs in patients with COVID-19 (Bozkurt et al, *HFSA/ACC/AHA Statement Addresses Concerns Re: Using RAAS Antagonists in COVID-19*, 2020). This remains an area of investigation and it is unclear how these medications affect patients with COVID-19.

Non-steroidal anti-inflammatory drugs (NSAIDs)

1. **Pathophysiology:**

    1. SARS-CoV-2 binds to cells via ACE2. ACE2 is upregulated by ibuprofen in animal models, and this might contribute to increased pathology (see "Angiotensin Converting Enzyme Inhibitors (ACE-I) and Angiotensin II Receptor Blockers (ARB)" section of this chapter).

2. **Recommendation:**

    1. Consider acetaminophen instead of NSAIDs if possible; risk / benefit should be discussed with patients and treatment team.

        1. Reports from France indicate possible increase in mortality with ibuprofen in COVID-19 infection, but these reports have not been corroborated (Fang et al, *Lancet Respir Med*, 2020; Day M, *BMJ*, 2020).
        2. WHO clarified on 3/20/20 it does not recommend avoiding NSAIDs as intially stated 3/18/20 (WHO, *COVID-19 Interim guidance*, March 2020).

Source: Brigham and Women's Hospital

COVID-19 Critical Care Clinical Guidelines

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