Concordance of Interleukin-6 Receptor Antagonist Prescribing In The Fraser Health Authority To British Columbia Coronavirus Disease 2019 Guidance

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Background

- Coronavirus Disease 2019 (COVID-19) produces a rapid increase in pro-inflammatory cytokines that is correlated with admission to intensive care unit (ICU), acute respiratory distress syndrome and death[1-3]
- The interleukin-6 receptor antagonists (IL-6 RAs), tocilizumab and sarilumab, reduce mortality and clinical deterioration in patients with COVID-19[4,5]
- The British Columbia COVID-19 Therapeutics Committee (BC-CTC) recommends the use of IL-6 RAs in critically-ill patients[6]
- Quality improvement evaluations reviewing concordance of IL-6 RAs to the BC-CTC guidance in the Fraser Health Authority (FHA) have not been performed to date

Objectives

Primary:

- Determine the percentage of patients prescribed an IL-6 RA for COVID-19 concordant to the BC-CTC recommendations

Secondary:

- Characterize the patients who received IL-6 RAs
- Determine in-hospital mortality, hospital and critical care length of stay (LOS)
- Report respiratory support free days after receiving an IL-6 RA
- Report clinical status using the World Health Organization (WHO) ordinal scale assessed on day of admission and day 14
- Describe adverse events associated with the use of IL-6 RAs

Methods

Design: Retrospective, cohort study of consecutive patients

Inclusion:

- Age ≥ 18 years
- Received IL-6 RAs at a FHA site from January to May 2021

Exclusion:

- Received IL-6 RAs for a non-COVID-19 related indication
- Incomplete charts or health records

Concordance definition:

- Correct indication:
  - Laboratory confirmed COVID-19; AND
  - Receiving high flow oxygen*; OR
  - Invasive/non-invasive ventilation; OR
  - Vasopressors/inotropes
- Correct dose:
  - Tocilizumab 8mg/kg or 400mg** IV x 1 dose; OR
  - Sarilumab 400mg IV x 1 dose
- Correct timing:
  - Within 24 hours of commencing oxygen/ventilatory support OR vasopressors/inotropes
- Absence of study exclusion criteria[5]:
  - ANC < 1.0 x 10^9/L
  - Platelets < 50 x 10^9/L
  - AST/ALT > 5 times upper limit
  - Admitted with COVID-19 for > 14 days
  - Other active infection
  - Immunosuppression

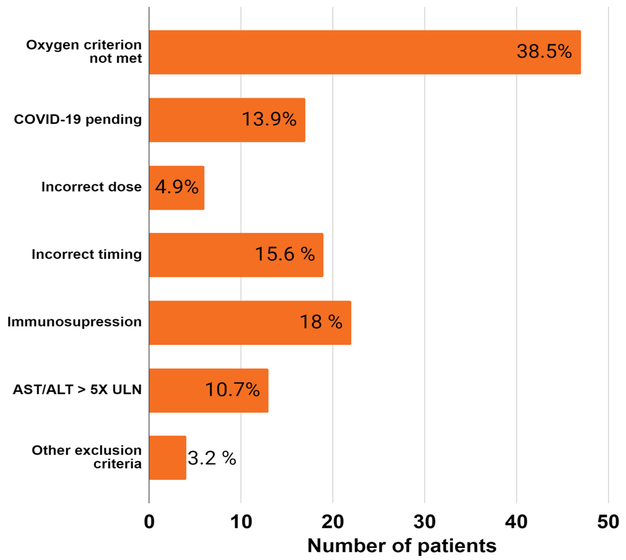
*Flow rate > 30 L/min and FiO_2 > 0.4

**From April 9 to May 31 due to limited tocilizumab supplies, 400mg IV x 1 was recommended by the BC-CTC

Results

- Of the 612 included patients, 490 patients (80.1%) received an IL-6 RA concordant with the BC-CTC guidance and 122 patients (19.9%) did not
- Reasons for discordance are presented in Figure 1

Figure 1. Reasons for Discordance (N=122)



- Of the 47 patients who did not meet the oxygen criterion, 27 patients progressed to high-flow
- All 17 COVID-19 pending patients returned as COVID-19 positive

Table 1. Patient Characteristics	N=612
Age, years (SD)	60 ± 15.1
Male, n (%)	391 (63.9)
Weight, kg (IQR)*	84.5 (70.2, 99.9)
Ethnicity, n (%)	
Caucasian	229 (37.4)
South Asian	215 (35.1)
Chinese	97 (9.2)
Other	112 (18.3)
Pregnant, n (%)	8 (1.3)
CRP, mcg/L (IQR)**	100.1 (54.8, 154.3)
Comorbidities, n (%)	
Hypertension	278 (45.6)
Cardiovascular Disease	241 (39.5)
Diabetes	221 (36.3)
Chronic Kidney Disease	63 (10.3)
Asthma	62 (10.1)
COPD	37 (6.1)
Dexamethasone co-administered, n (%)	610 (99.7)

*n=556

**n= 582

Results

Table 2. Secondary Endpoints	N=612
In-hospital mortality, n (%)	113 (18.5)
Hospital LOS, days (IQR)	13.6 (9, 25)
Critical care LOS*, days (IQR)	6.5 (3.3, 13.7)
Respiratory support free days, days (IQR)	1 (0, 2)
WHO ordinal scale on admission (IQR)	4 (4, 5)
WHO ordinal scale at day 14 (IQR)	4 (1, 5)
Adverse Events	188 (30.7)
Microbiologically confirmed infection£, n (%)	136 (22.2)
Transaminitis‼, n (%)	33 (5.4)
Infusion related reactions$, n (%)	19 (3.1)
Gastrointestinal perforation€, n (%)	0 (0)

*n=453

£ Body fluid culture for bacteria, viral (other than COVID-19), fungal or mycobacterium until hospital discharge or up to 4 weeks after the infusion

‼ Presence of change in AST/ALT levels until hospital discharge or up to 4 weeks after the infusion date, as defined by Kullak-Ublick GA, et al.[7]

$ Hypertension (>180/120 mmHg), skin reactions (rash, pruritus, urticaria), or anaphylaxis during or up to 24 hours after the infusion

€ Gastrointestinal perforation up to 2 weeks after the infusion date confirmed by computed tomography of the abdomen or endoscopy/laparotomy

Discussion

- While not meeting the high-flow oxygen criterion was deemed discordant in this study, the RECOVERY trial demonstrated a mortality benefit from tocilizumab in patients on all forms of supplemental oxygen[4]
- While patients who met exclusion criteria were not explicitly contraindicated by the BC-CTC guidance, the efficacy of IL-6 RAs in these patients has not been prospectively evaluated to date
  - In a matched cohort study, tocilizumab use amongst COVID-19 solid organ transplant patients appeared to be safe but did not decrease 90-day mortality[8]
- In-hospital mortality was significantly lower than that reported in the REMAP-CAP trial (28%),[5] but similar to that previously reported in lower mainland critical care units early in the pandemic (15.4%)[9]
  - Elucidating the reasons for this lower mortality rate should be considered in future studies
- Adverse events in our study were higher than that reported in literature, largely driven by microbiologically confirmed infection[4,5]
  - This is hypothesis generating as causation cannot be determined

Limitations

- Data collection relies on complete documentation in medical records
- Actual time of prescribing could not be confirmed in all cases, therefore the time of order entry was used as a surrogate marker and may impact concordance assessments
- Microbiologically confirmed infections may not translate into clinical infections and may overestimate infections in this study

Conclusions

- While the majority of patients received an IL-6 RA concordant with the BC-CTC guidance, opportunities to improve prescribing exist
- Infections and transaminitis were observed after the administration of IL-6 RAs, but causation cannot be determined

References:

1) Peer J 2020;8:1-19
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7) Drug Saf 2014;37:S57-62
8) Am J Transplant 2020;20:3198-3205
9) CMAJ 2020;192 (26):E694-E701