Interferons (IFN)

A Review of Pertinent Drug Information for SARS-CoV-2

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Data as of May 13, 2020

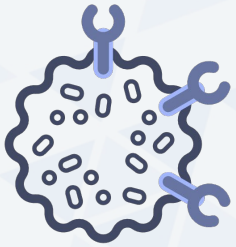
Mechanism of Action

Viruses

- Infect host cells
- SARS-CoV-2 enters through the angiotensin-converting enzyme 2 (ACE-2) receptor

Host cells

- Recognize viral components
- Produce and release interferons (family of cytokines)



Interferons

- Bind to specific plasma membrane receptors on most cell types

Intracellular events

- Positive: activates JAK-STAT signaling pathway
- Negative: recruits pro-inflammatory mediators (e.g., macrophages)

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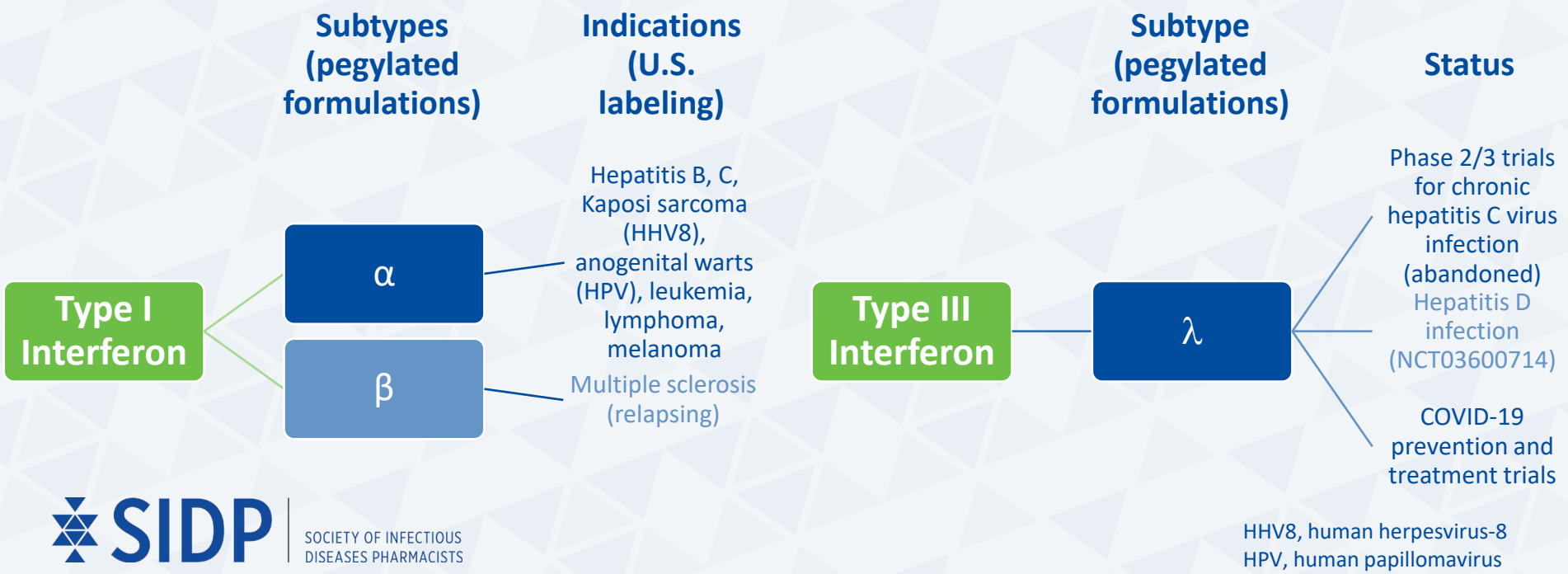
IFN, interferon
JAK, Janus kinase
STAT, signal transducer and activator of transcription

Sallard E, et al. Antiviral Research. 2020;178. https://doi.org/10.1016/j.antiviral.2020.104791.

Interferons Overview



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HHV8, human herpesvirus-8
HPV, human papillomavirus

Lexicomp [Internet]. Wolters Kluwer Health, Inc. Available at: http://online.lexi.com. Accessed May 13, 2020.

In Vitro Data

IFN α or β

- IFNβ is a **more potent** inhibitor of coronaviruses than IFNα[1]
- **SARS-CoV-2 *may* be more sensitive to IFNα**[2]

β-1a or β-1b

- IFNβ-1a more potent for SARS-CoV[3]
- IFNβ-1b more potent for MERS-CoV[4,5]

IFNβ1 and IFNλ

Protective activity in the lungs[6,7]

Caveat: SARS-CoV-2 infection weakly induces IFN types I-III expression compared to SARS-CoV (*ex vivo* human lung tissues)[8]

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[1]Stockman LJ, et al. PLoS Med. 2006. https://doi.org/10.1371/journal.pmed.0030343.
[2]Lokugamage KG, et al. BioRxiv. 2020. https://doi.org/10.1101/2020.03.07.982264.
[3]Hensley LE, et al. Emerg Infect Dis. 2004;10(2):317-319.
[4]Chan JF, et al. J Infect. 2013;67(6):606-16.
[5]Hart BJ, et al. J Gen Virol. 2014;95(3):571-77.
[6]Bellingan G, et al. Lancet Respir Med. 2(2):98-107.
[7]Kotenko SV, et al. Nat Immunol. 2003;4:69-77.
[8]Chu H, et al. Clin Infect Dis. 2020. https://doi.org/10.1093/cid/ciaa410.

In Vitro Data

SARS-CoV
(Ref 1-3)

- IFNα and **IFNβ-1a/b** inhibits virus replication, especially when added to Vero cells (monkey kidney epithelial cells) pre-incubation (i.e., prophylaxis) or alone in Caco2 cells (human intestinal epithelial cell line)
- **Synergy** demonstrated with IFNβ-1a and ribavirin[2]

MERS-CoV
(Ref 4-6)

- **IFNβ (1b)** showed the strongest virus inhibition compared to other IFN tested in Vero cells and Calu-3 cells (human lung epithelial cell line)
- Combination with **mycophenolic acid** lowered the EC_{50} of each drug by 1-3 times[4]

SARS-CoV-2
(Ref 7)

- Infection **weakly induced** IFN (types 1-3) expression compared to SARS-CoV in *ex vivo* human lung tissues

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[1]Cinatl J, et al. Lancet. 2003;362(9380):293-94.
[2]Chen F, et al. J Clin Virol. 2004;31(1):69-75.
[3]Hensley LE, et al. Emerg Infect Dis. 2004;10(2):317-19.
[4]Chan JF, et al. J Infect. 2013;67(6):606-16.
[5]Hart BJ, et al. J Gen Virol. 2014;95(3):571-77.
[6]Sheahan TP, et al. Nat Commun. 2020;11(1):222.
[7]Chu H, et al. Clin Infect Dis. 2020. https://doi.org/10.1093/cid/ciaa410.

In Vivo Animal Data

SARS-CoV
(Ref 1,2)

- In macaques, **PEG-IFNα** ⇩ virus replication, viral antigen expression, and pulmonary damage when used as prophylaxis; less effective for treatment
- In aged macaques, **IFNα** ⇩ pathology with no effect on virus replication; also ⇩ inflammatory gene expression

MERS-CoV
(Ref 3,4)

- In rhesus macaques, **IFNα-2b with ribavirin** ⇩ virus replication, moderated host response, improved clinical outcomes
- In marmosets, **IFNβ-1b** improve clinical, radiological, and pathological findings

ARDS
(Ref 5)

- In mice with ARDS, **IFNβ-1** subcutaneously improved survival and restored alveolar macrophage function

ARDS, acute respiratory distress syndrome

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[1]Haagmans BL, et al. Nat Med. 2004;10(3):290-93.
[2]Smits SL, et al. PLoS Pathog. 2010;6(2):e1000756.
[3]Falzarano D, et al. Nat Med. 2013;19(10):1313-17.
[4]Chan JF, et al. J Infect. 2013;67(6):606-16.
[5]Hiruma T, et al. Am J Respir Cell Mol Biol. 2018;59(1):45-55.

SARS-CoV Clinical Data

Population	Interferon (IFN)	Combination	Outcome(s)
Hospitalized adults with clinical signs and symptoms of SARS in China (N = 190)	• IFNα 3 million units intramuscularly daily • Three of four treatment groups received IFNα	• Fluoroquinolone and azithromycin • ± corticosteroid	• Two out of 30 (6%) patients who definitively received IFN died • Unclear how many received IFN in other treatment groups

INTERFERON ALFA INCONCLUSIVE FOR SARS TREATMENT

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Zhao Z, et al. J Med Microbiol. 2003;52(8):715-20.

MERS-CoV Observational Data

Study Type	Interferon (IFN)	Combination	Outcome(s)
Case series[1-4]	IFNα-2a and IFNα-2b subcutaneously weekly for two weeks	Oral ribavirin with loading doses	• 8 of 24 (33%) patients died across four case series • Delayed time to treatment was observed in patients who died
Small cohorts[5,6]			
N = 32 • IFNα-2a: 13 • IFNβ-1a: 11	• IFNα-2a 180 mcg subcutaneously once weekly • IFNβ-1a44 mcg subcutaneously three times weekly	Ribavirin 2 g loading dose, then 600 mg orally every 12 hours	• IFNα-2a: 85% (n = 11) died • IFNβ-1a: 64% (n = 7) died
• N = 44	• PEG-IFNα-2a subcutaneously	Oral ribavirin for 8-10 days	• Improved 14-day but not 28-day survival

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[1]Al-Tawfiq JA, et al. Int J Infect Dis. 2014;20:42-46.
[2]Khalid M, et al. Ann Saudi Med. 2014;34(5):396-400.
[3]Khalid M, et al. Antivir Ther. 2015;20(1):87-91.
[4]Khalid I, et al. Respir Care. 2016;61(3):340-348.
[5]Shalhoub S, et al. J Antimicrob Chemother. 2015;70(7):2129-2132.
[6]Omrani AS, et al. Lancet Infect Dis. 2014;14(11):1090-1095.

MERS-CoV Observational Data

Study Type	Interferon (IFN)	Combination	Outcome(s)
Retrospective cohort of critically ill patients (N = 349)	Three treatment groups: • PEG-IFNα-2a 180 mcg subcutaneously once weekly x 2 weeks • PEG-IFNα-2b 1.5 mcg/kg subcutaneously once weekly x 2 weeks • IFNβ-1a 44 mg subcutaneously three times weekly Comparator group without IFN/ribavirin treatment	Oral ribavirin for 8-10 days with loading doses	• n = 117 received IFN/ribavirin combination, and among this group 58% of patients received **PEG-IFNα-2a** • Median time to IFN administration was 2 days following ICU admission • Unadjusted in-hospital, 28- and 90-day mortality rates were higher in IFN/ribavirin vs. no IFN/ribavirin • No difference in 90-day mortality nor in viral clearance in adjusted analyses • No differences in safety endpoints

IFN + ORAL RIBAVIRIN COMBINATION INCONCLUSIVE FOR MERS TREATMENT

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Arabi YM, et al. Clin Infect Dis. 2020;70(9):1837-1844.

MERS-CoV Observational Data

Study Type	Interferon (IFN)	Combination	Outcome(s)
Case report[1] (Greece)	**PEG-IFNα** 180 mcg subcutaneously once weekly for 12 days	• Lopinavir/ritonavir 400/100 mg orally twice daily for 12 days • Ribavirin orally for 8 days (2000 mg loading dose followed by 1200 mg every 8 hours)	• IFN administration was on day 13 following MERS-CoV detection • Kidney function improved on day 21, fever resolved on day 22 • In-hospital mortality from colon adenocarcinoma (subsequently diagnosed) and septic shock
Case report[2] (South Korea)	**PEG-IFNα-2a** 180 mcg subcutaneously for one dose	• Lopinavir/ritonavir 400/10 mg orally twice daily for 7 days • Ribavirin orally for 7 days (2000 mg loading dose followed by 1200 mg every 8 hours)	• Complete recovery and hospital discharge

IFN + LOPINAVIR/R + RIBAVIRIN TRIPLE COMBINATION HIGHLY INCONCLUSIVE FOR MERS-CoV INFECTIONS

[1]Spanakis N, et al. Int J Antimicrob Agents. 2014;44(6):528-532.
[2]Kim UJ, et al. Antivir Ther. 2016;21(5):455-459.

Phase II Clinical Trial

Study Design/Population

- Multicenter, prospective, open-label, randomized 2:1
- Hospitalized adults with COVID-19
- **Mild to moderate disease** (baseline SOFA scores of 0 and NEWS2 scores of ≤2)

Intervention/Comparator

- **Lopinavir/r** 400/100 mg by mouth every 12 hours + **ribavirin** 400 mg by mouth every 12 hours for 14 days + **IFN β-1b** 8 million IU subcutaneously on alternate days for 1-3 doses depending on time of enrollment (n = 86)
- Lopinavir/r 400/100 mg by mouth every 12 hours for 14 days (n = 41)
- Median time to drug administration was 5 days from symptom onset and combination must be initiated **within 48 hours of hospital admission**
- IFN was omitted in patients who presented ≥7 days after symptom onset to **avoid pro-inflammatory effects** (n = 52 received IFN)

Outcomes

- **Time to negative nasopharyngeal swab**: median of **6.5 vs. 12.5 days** ($p < 0.0001$) in IFN combination vs. monotherapy group, respectively
- Safety endpoints: no deaths; self-limiting nausea and diarrhea and balanced in both groups

Hospital length of stay was **shorter** in IFN-combination group at 8 vs. 15 days ($p = 0.003$)

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NEWS2, National Early Warning Score 2
SOFA, Sequential Organ Failure Assessment

Hung IF, et al. Lancet. 2020. https://doi.org/10.1016/S0140-6736(20)31042-4.

Interferon Dosing[1]

Expert panel[2] recommends **against** the use of interferons for COVID-19 treatment, except in a clinical trial context.

IFN β-1b
8 million units (0.25 mg) subcutaneously on alternate days for 1-3 doses

Lopinavir/ ritonavir
400/100 mg by mouth every 12 hours for 14 days

Ribavirin
400 mg by mouth every 12 hours for 14 days

Initiated within 48 hours of hospital admission and <7 days from symptom onset

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[1]Hung IF, et al. Lancet. 2020. https://doi.org/10.1016/S0140-6736(20)31042-4
[2]COVID-19 Treatment Guidelines Panel. National Institutes of Health. https://covid19treatmentguidelines.nih.gov

Interferon Products

Generic Name	Trade Name	Dosage Forms and Strengths	Administration Route
PEG-interferon α-2a	*Pegasys*	• Solution for injection: 180 mcg/mL, 180 mcg/0.5 mL, 135 mcg/0.5 mL	Subcutaneous
Interferon α-2b	*Intron A*	• Powder for solution: 10, 18, 50 million units • Solution for injection: 6 and 10 million units/mL	Subcutaneous, intramuscular, intravenous, intralesional
PEG-interferon α-2b	*PegIntron, Sylatron*	Powder for solution (concentrations after reconstitution): • *PegIntron*: 50, 80, 120, 150 mcg per 0.5 mL • Sylatron: 40, 60, 120 mcg per 0.1 mL	Subcutaneous
Interferon α-n3	*Alferon N*	• Solution for injection: 5 million units/mL	Intralesional
Interferon β-1a	*Avonex*	• Powder for solution: 33 mcg • Solution for injection: 30 mcg/0.5 mL	Intramuscular
	Rebif	• Solution for injection: 8.8 mcg/0.2 mL, 22 mcg/0.5 mL, 44 mcg/0.5 mL	Subcutaneous
PEG-interferon β-1a	*Plegridy*	• Solution for injection: 63, 94, 125 mcg/0.5 mL	Subcutaneous
Interferon β-1b	*Betaseron, Extavia*	• Powder for solution: 0.3 mg	Subcutaneous

Lexicomp [Internet]. Wolters Kluwer Health, Inc. Available at: http://online.lexi.com. Accessed May 13, 2020.

Ongoing Clinical Trials

Prevention in medical staff (NCT04320238)

Recruiting

- Phase 3 single-center, open-label non-randomized trial
- **Interferon α-1b intranasally** 2-3 drops per nostril four times daily (low-risk) vs. interferon α-1b intranasally and thymosin α1 subcutaneously once weekly (high-risk)
- 1° outcome: new onset COVID-19 (assessed up to 6 weeks)

Prevention in high-risk patients (NCT04344600)

Not yet recruiting

- Phase 2 single-center, single-blind (participant), placebo-controlled, randomized trial
- **PEG-IFN λ–1a** 180 mcg subcutaneously once weekly x 2 doses vs. placebo
- 1° outcome: proportion with no SARS-CoV-2 infection (up to 28 days)

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ClinicalTrials.gov [Internet]. U.S. National Library of Medicine. Available at: https://clinicaltrials.gov. Accessed May 13, 2020.

Ongoing Clinical Trials

Mild to moderate COVID-19 (ChiCTR2000029387)[1]

Recruiting

- Open-label, single-center, randomized trial
- Interferon α-1b 5 million units (50 mcg/dose) **atomized inhalation** twice daily with either ribavirin or lopinavir/r or ribavirin and lopinavir/r for 14 days
- 1° outcome: two consecutive RNA results

Moderate to severe COVID-19 (NCT04343768)[2]

Completed

- Phase 2 open-label randomized trial
- Interferon β-1a or 1b (unspecified route) with hydroxychloroquine and lopinavir/r vs. hydroxychloroquine and lopinavir/r
- 1° outcome: time to clinical improvement defined by WHO COVID-19 R&D (7-point ordinal scale)

Hospitalized COVID-19 (NCT04350281)[2]

Recruiting

- Phase 2 open-label randomized trial
- Interferon β-1b 0.25 mg subcutaneously once daily with hydroxychloroquine on days 1-3 and standard of care vs. hydroxychloroquine and standard of care
- 1° outcome: time to negative nasopharyngeal RT-PCR

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[1]Zeng Y, et al. Chin Med J (Engl). 2020;133(9):1132-34. https://doi.org/10.1097/CM9.0000000000000790.
[2]ClinicalTrials.gov [Internet]. U.S. National Library of Medicine. Available at: https://clinicaltrials.gov. Accessed May 13, 2020.

Ongoing Clinical Trials

Hospitalized COVID-19
(NCT04315948)[1]
Recruiting

World Health Organization

- Phase 3 multicenter, adaptive, open-label randomized trial
- Interferon β-1a 44 mcg subcutaneously on days 1, 3, 6 with lopinavir/r vs. three other experimental groups and standard of care (control)
- 1° outcome: clinical status at day 15 (7-point ordinal scale defined by WHO COVID-19 R&D)

Hospitalized COVID-19
(NCT04343976)[1]
Not yet recruiting

- Phase 2 single-center, open-label, randomized trial
- **PEG-IFN λ** 180 mcg subcutaneously (frequency unspecified) vs. standard of care supportive treatment
- 1° outcome: undetectable SARS-CoV-2 PCR test result at day 7

Hospitalized **MERS-CoV**
(NCT02845843)[2]
Recruiting

- Phase 2/3 multicenter, placebo-controlled, double-blind randomized trial
- Interferon β-1b 0.25 mg subcutaneously every other day with lopinavir/r for 14 days vs. placebo
- 1° outcome: 90-day mortality

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[1]ClinicalTrials.gov [Internet]. U.S. National Library of Medicine. Available at: https://clinicaltrials.gov. Accessed May 13, 2020.
[2]Arabi YM, et al. Trials. 2020;21(1):8. https://doi.org/10.1186/s13063-019-3846-x.

Adverse Effects

Flu-like symptoms

Fevers, chills, myalgias

Hematological toxicities

⇓ lympho-cytes
⇓ platelets

Hepatotoxicity

⇑ trans-aminases

Neuropsychiatric disorders

Depression, suicidal ideation

IFNβ is better tolerated than IFNα
Adverse effects are notably lower with pegylated IFNλ1

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Lexicomp [Internet]. Wolters Kluwer Health, Inc. Available at: http://online.lexi.com. Accessed May 13, 2020.

Special Considerations

- **Drug interactions:** potential for added toxicity with other immunomodulators and chemotherapies (avoid with cladribine)
- **Pregnancy:** registries data have not observed an increased risk or pattern of major birth defects, preterm births, or decreased birth weight
- **Pediatrics:** some (limited) data for respiratory viral infection treatment with topical/aerosolized IFN

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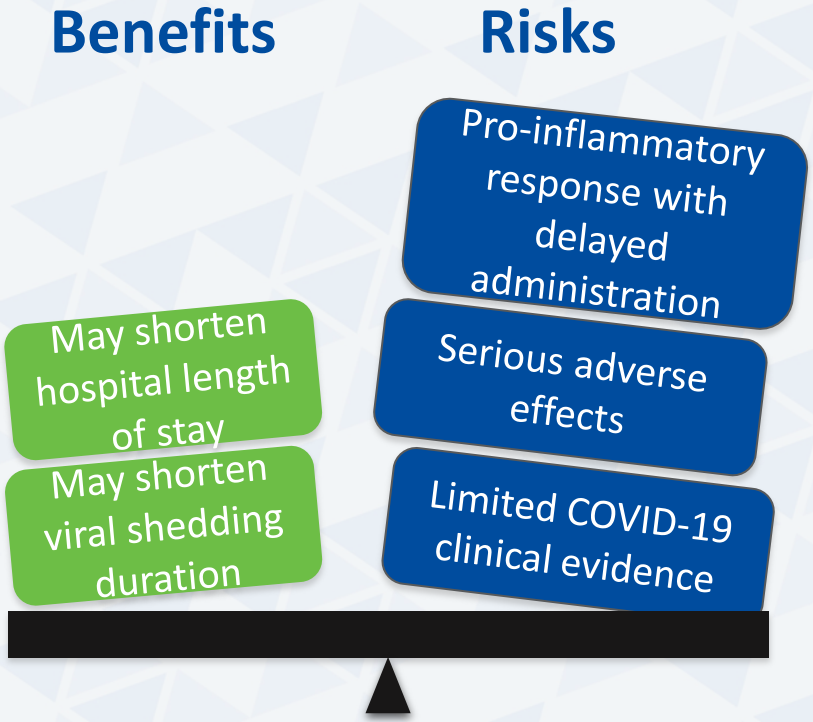
Lexicomp [Internet]. Wolters Kluwer Health, Inc. Available at: http://online.lexi.com. Accessed May 13, 2020.

Clinical Pearls



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Summary

- **Interferons** for COVID-19 treatment is **only** to be given in a **clinical trial context**
- Current clinical evidence for COVID-19 treatment is one phase 2 randomized trial in adults with mild to moderate disease
- Additional trials are under way and needed to determine whether **early** interferon initiation **in combination** with other antivirals improves COVID-19 clinical outcomes

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