Interferons (IFN)

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

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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)

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

Subtypes (pegylated formulations)

Type I Interferon
- \( \alpha \)
- \( \beta \)

Type III Interferon
- \( \lambda \)

Indications (U.S. labeling)

Hepatitis B, C, Kaposi sarcoma (HHV8), anogenital warts (HPV), leukemia, lymphoma, melanoma

Multiple sclerosis (relapsing)

Status

Type I Interferon
- Phase 2/3 trials for chronic hepatitis C virus infection (abandoned)
- Hepatitis D infection (NCT03600714)
- COVID-19 prevention and treatment trials

HHV8, human herpesvirus-8
HPV, human papillomavirus

**In Vitro Data**

- IFNβ is a **more potent** inhibitor of coronaviruses than IFNα\(^1\)
- **SARS-CoV-2 may be more sensitive to IFNα**\(^2\)
  - 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](https://doi.org/10.1371/journal.pmed.0030343).


**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

**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)

**SARS-CoV-2** (Ref 7)
- Infection weakly induced IFN (types 1-3) expression compared to SARS-CoV in ex vivo human lung tissues

**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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**SARS-CoV**

**Clinical Data**

<table>
<thead>
<tr>
<th>Population</th>
<th>Interferon (IFN)</th>
<th>Combination</th>
<th>Outcome(s)</th>
</tr>
</thead>
</table>
| 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**

# MERS-CoV Observational Data

<table>
<thead>
<tr>
<th>Study Type</th>
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| 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\(^5\)\(^,\)\(^6\) | IFNα-2a 180 mcg subcutaneously once weekly  
IFNβ-1a 44 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 = 32  
• IFNα-2a: 13  
• IFNβ-1a: 11 | PEG-IFNα-2a subcutaneously | Oral ribavirin for 8-10 days | • Improved 14-day but not 28-day survival |

### MERS-CoV Observational Data

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| 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**

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

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

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

NEWS2, National Early Warning Score 2
SOFA, Sequential Organ Failure Assessment
Expert panel\(^2\) recommends **against** the use of interferons for COVID-19 treatment, except in a clinical trial context.

**Interferon Dosing**\(^1\)

- **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

\(^1\)Hung IF, et al. Lancet. 2020. [https://doi.org/10.1016/S0140-6736(20)31042-4](https://doi.org/10.1016/S0140-6736(20)31042-4)

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Dosage Forms and Strengths</th>
<th>Administration Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG-interferon α-2a</td>
<td>Pegasys</td>
<td>• Solution for injection: 180 mcg/mL, 180 mcg/0.5 mL, 135 mcg/0.5 mL</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td>Interferon α-2b</td>
<td>Intron A</td>
<td>• Powder for solution: 10, 18, 50 million units</td>
<td>Subcutaneous, intramuscular, intravenous, intralesional</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Solution for injection: 6 and 10 million units/mL</td>
<td></td>
</tr>
</tbody>
</table>
| 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                                               | Intraleosional                        |
| 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                          |

**Ongoing Clinical Trials**

**Prevention in medical staff**
(NCT04320238)

- 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)

- 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)

### Ongoing Clinical Trials

#### Mild to moderate COVID-19 (ChiCTR2000029387)
- **Recruiting**
- **Trial Type:** Open-label, single-center, randomized trial
- **Intervention:** 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
- **Primary Outcome:** Two consecutive RNA results

#### Moderate to severe COVID-19 (NCT04343768)
- **Completed**
- **Trial Type:** Phase 2 open-label randomized trial
- **Interventions:** Interferon β-1a or 1b (unspecified route) with hydroxychloroquine and lopinavir/r vs. hydroxychloroquine and lopinavir/r
- **Primary Outcome:** Time to clinical improvement defined by WHO COVID-19 R&D (7-point ordinal scale)

#### Hospitalized COVID-19 (NCT04350281)
- **Recruiting**
- **Trial Type:** Phase 2 open-label randomized trial
- **Interventions:** 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
- **Primary Outcome:** Time to negative nasopharyngeal RT-PCR

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Ongoing Clinical Trials

Hospitalized COVID-19 (NCT04315948)¹

- 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)
- 1º outcome: clinical status at day 15 (7-point ordinal scale defined by WHO COVID-19 R&D)

Recruiting

Hospitalized COVID-19 (NCT04343976)¹

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

Not yet recruiting

Hospitalized MERS-CoV (NCT02845843)²

- 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
- 1º outcome: 90-day mortality

Recruiting

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

Clinical Pearls

Benefits
- May shorten hospital length of stay
- May shorten viral shedding duration

Risks
- Pro-inflammatory response with delayed administration
- Serious adverse effects
- Limited COVID-19 clinical evidence

SOCIETY OF INFECTIOUS DISEASES PHARMACISTS
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
Interferons (IFN)

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