Table 4b. Interferons: Selected Clinical Data

Last Updated: December 16, 2021

The clinical trials described in this table do not represent all the trials that the Panel reviewed while developing the recommendations for interferons. The studies summarized below are the randomized controlled trials that have had the greatest impact on the Panel's recommendations.

Methods	Results	Limitations and Interpretation
ACTT-3: Multinational, Double-Blind RCT of Interferon Beta-1a and Remdesivir in Hospitalized Adults With COVID-19[1]		

Key Inclusion Criteria:
• Evidence of pneumonia (radiographic infiltrates, SpO_2 ≤94% on room air, or supplemental oxygen)
• No MV required
Key Exclusion Criteria:
• AST or ALT >5 times ULN
• Impaired renal function
• Anticipated hospital discharge or transfer within 72 hours
Interventions:
• RDV 200 mg IV on Day 1, then RDV 100 mg IV once daily for 9 days plus IFN beta-1a 44 µg SQ every other day for up to 4 doses (n = 487)
• RDV 200 mg IV on Day 1, then RDV 100 mg IV once daily for 9 days plus placebo (n = 482)
Primary Endpoint:
• Time to recovery by Day 28
Key Secondary Endpoints:
• Clinical status at Day 14, as measured by an OS
• Mortality by Day 28
	Participant Characteristics:
	• Mean age 59 years; 38% were aged ≥65 years
	• 58% men; 32% Latino, 60% White, 17% Black
	• Mean of 8.6 days of symptoms before enrollment
	• 90% had ≥1 comorbidity; 58% with HTN; 58% with obesity; 37% with DM
	Primary Outcome:
	• Median time to recovery for both arms was 5 days (rate ratio 0.99; 95% CI, 0.87–1.13; $P = 0.88$).
	  • In patients on high-flow oxygen or NIV (OS6) at baseline, median time to recovery was >28 days in IFN beta-1a arm and 9 days in placebo arm (rate ratio 0.40; 95% CI, 0.22–0.75; $P = 0.0031$).
	Secondary Outcomes:
	• No difference between arms in clinical improvement at 14 days (OR 1.01; 95% CI, 0.79–1.28).
	• No difference between arms in mortality by Day 28 in:
	  • All patients: 5% vs. 3% (HR 1.33; 95% CI, 0.69–2.55)
	  • Patients with OS6 at baseline: 21% vs. 12% (HR 1.74; 95% CI, 0.51–5.93)
		Key Limitation:
		• OS6 patients were excluded after 270 patients were enrolled because of an increased frequency of AEs in this group
		Interpretation:
		• There was no clinical benefit of IFN beta-1a plus RDV in hospitalized patients compared to RDV alone.
		• The use of IFN beta-1a was associated with worse outcomes among patients who were OS6 at baseline.

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Methods	Results	Limitations and Interpretation
WHO Solidarity Trial: Multinational, Open-Label, Adaptive RCT of IV or SQ Interferon Beta-1a or Other Repurposed Drugs in Hospitalized Adults With COVID-19[2]		
Key Inclusion Criteria: • Diagnosis of COVID-19 • Not expected to be transferred elsewhere within 72 hours **Interventions:** • IFN beta-1a 44 µg SQ on day of randomization, Day 3, and Day 6 (n = 1,656) • IFN beta-1a 10 µg IV daily for 6 days for patients on high-flow oxygen, ventilation, or ECMO (n = 394) • IFN beta-1a (either SQ or IV) and LPV/RTV 400 mg/50 mg twice daily for 14 days (n = 651) • Local SOC (n = 2,050) **Primary Endpoint:** • In-hospital mortality **Key Secondary Endpoint:** • Initiation of ventilation	**Participant Characteristics:** • 35% aged <50 years; 19% aged ≥70 years; 63% men • 70% on supplemental oxygen; 7% on ventilation • Approximately 50% received corticosteroids during the study **Primary Outcomes:** • In-hospital mortality was 11.9% for combined IFN beta-1a arms and 10.5% in SOC arm (rate ratio 1.16; 95% CI, 0.96–1.39). • For IFN beta-1a only (without LPV/RTV) recipients vs. SOC recipients, rate ratio was 1.12 (95% CI, 0.83–1.51). • Among those on ventilation at entry, age-stratified rate ratio for in-hospital mortality was 1.40 (95% CI, 0.93–2.11). **Secondary Outcome:** • 10% initiated ventilation in the combined IFN beta-1a arms and SOC arm.	**Key Limitations:** • Open-label study • IFN beta-1a given as IV or SQ formulations at different doses **Interpretation:** • IFN beta-1a does not improve mortality for hospitalized patients.

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Methods	Results	Limitations and Interpretation
DisCoVeRy Solidarity Trial Add-On: Open-Label, Adaptive RCT of SQ Interferon Beta-1a Plus Lopinavir/Ritonavir, Lopinavir/Ritonavir, or Hydroxychloroquine in Hospitalized Adults With COVID-19 in France[3]		

Key Inclusion Criteria:
• Positive PCR result for SARS-CoV-2
• Patients had pulmonary rales or crackles with SpO_2 ≤94% or they required supplemental oxygen
Interventions:
• IFN beta-1a 44 ug SQ on Days 1, 3, and 6 plus LPV/RTV 400 mg/100 mg PO twice daily for 14 days plus SOC (n = 145)
• LPV/RTV 400 mg/100 mg PO twice daily for 14 days plus SOC (n = 145)
• HCQ 400 mg twice on Day 1, then HCQ 400 mg daily for 9 days plus SOC (n = 145)
• SOC alone, which included corticosteroids, anticoagulants, or immunomodulatory agents but not antivirals (n = 148)
Primary Endpoint:
• Clinical status at Day 15, as measured by an OS
Key Secondary Endpoints:
• Clinical status at Day 29
• Rate of SARS-CoV-2 viral clearance
• Time to SARS-CoV-2 viral clearance
• Time to improvement of 2 OS categories
• Time to hospital discharge
	Participant Characteristics:
	• Median age 63 years; 72% men
	• 29% were obese; 26% with chronic cardiac disease; 22% with DM
	• 36% had severe disease
	• Median of 9 days from symptom onset to randomization
	• 30% received steroids during the study
	Primary Outcome:
	• No difference in clinical status at Day 15 for any intervention compared to SOC:
	  • IFN beta-1a plus LPV/RTV: aOR 0.69 (95% CI, 0.45–1.04; *P* = 0.08)
	  • LPV/RTV: aOR 0.83 (95% CI, 0.55–1.26; *P* = 0.39)
	  • HCQ: aOR 0.93 (95% CI, 0.62–1.41; *P* = 0.75)
	Secondary Outcomes:
	• No difference in clinical status at Day 29 between the arms.
	• No difference in rate and time to SARS-CoV-2 viral clearance between the arms.
	• Time to 2 OS-category improvement and hospital discharge by Day 29 was longer in LPV/RTV plus IFN beta-1a and LPV/RTV arms than in SOC arm.
		Key Limitations:
		• Open-label study
		• Most patients had moderate disease
		• No IFN beta-1a arm without LPV/RTV
		• Study stopped early for futility
		Interpretation:
		• Compared to SOC alone, the use of IFN-beta-1a plus LPV/RTV did not improve clinical status, rate of viral clearance, or time to viral clearance in hospitalized patients with COVID-19.

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Methods	Results	Limitations and Interpretation
Single-Blind RCT of Peginterferon Lambda-1a for Treatment of Outpatients With Uncomplicated COVID-19 in the United States[4]		

Key Inclusion Criteria:
• Aged 18–65 years
• Asymptomatic or symptomatic
• Positive RT-PCR result for SARS-CoV-2 within 72 hours of enrollment
Key Exclusion Criteria:
• Current or imminent hospitalization
• Respiratory rate >20 breaths/min
• SpO_2 <94% on room air
• Decompensated liver disease
Interventions:
• Single dose of PEG-IFN lambda-1a 180 µg SQ (n = 60)
• Placebo (n = 60)
Primary Endpoint:
• Time to first negative SARS-CoV-2 RT-PCR result
Key Secondary Endpoints:
• Hospitalizations by Day 28
• Time to complete symptom resolution
	Participant Characteristics:
	• Median age 36 years; 42% women; 63% Latinx, 28% White
	• 7% were asymptomatic
	• Median of 5 days of symptoms before randomization
	Primary Outcome:
	• Median time to cessation of viral shedding was 7 days in both arms (aHR 0.81; 95% CI, 0.56–1.19; *P* = 0.29).
	Secondary Outcomes:
	• No difference between PEG-IFN lambda-1a and placebo arms in:
	  • Proportion of patients hospitalized by Day 28: 3.3% for each arm
	  • Time to resolution of symptoms: 8 days vs. 9 days (HR 0.94; 95% CI, 0.64–1.39)
	Other Outcomes:
	• Patients who received PEG-IFN lambda-1a were more likely to have transaminase elevations than patients who received placebo (25% vs. 8%; *P* = 0.027).
		Key Limitation:
		• Small sample size
		Interpretation:
		• PEG-IFN lambda-1a provided no virologic or clinical benefit compared to placebo among outpatients with uncomplicated COVID-19.

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Methods	Results	Limitations and Interpretation
Double-Blind RCT of Peginterferon Lambda in Outpatients With Laboratory-Confirmed COVID-19 in Canada[5]		
Key Inclusion Criteria: • Positive SARS-CoV-2 PCR result • Patients were within 7 days of symptom onset, or, if asymptomatic, were within 7 days of first positive SARS-CoV-2 test result **Key Exclusion Criterion:** • Immunosuppression or condition that could be worsened by PEG-IFN lambda **Interventions:** • Single dose of PEG-IFN lambda 180 µg SQ (n = 30) • Placebo (n = 30) **Primary Endpoint:** • Proportion of participants with negative nasal mid-turbinate swab for SARS-CoV-2 at Day 7 **Key Secondary Endpoints:** • Quantitative change in SARS-CoV-2 RNA over time • Hospitalizations by Day 14	**Participant Characteristics:** • Median age 46 years; 58% women; 52% White • 19% were asymptomatic • Mean of 4.5 days of symptoms before randomization **Primary Outcome:** • 80% in PEG-IFN lambda arm and 63% in placebo arms were negative for SARS-CoV-2 RNA at Day 7 ($P = 0.15$). **Secondary Outcomes:** • VL decline by Day 7 was greater in PEG-IFN lambda arm than in placebo arm ($P = 0.0041$). • 1 participant in each arm was admitted to the hospital by Day 14. **Other Outcomes:** • 3 participants in each arm had mild elevation of aminotransferase concentrations. Increase was greater in PEG-IFN lambda arm.	**Key Limitation:** • Small sample size **Interpretation:** • PEG-IFN lambda may accelerate VL decline and clearance in outpatients with COVID-19; however, the clinical significance of this finding is unclear.

Key: AE = adverse event; ALT = alanine transaminase; AST = aspartate aminotransferase; DM = diabetes mellitus; ECMO = extracorporeal membrane oxygenation; HCQ = hydroxychloroquine; HTN = hypertension; IFN = interferon; IV = intravenous; LPV/RTV = lopinavir/ritonavir; MV = mechanical ventilation; NIV = noninvasive ventilation; OS = ordinal scale; the Panel = the COVID-19 Treatment Guidelines Panel; PCR = polymerase chain reaction; PEG-IFN = pegylated interferon; RCT = randomized controlled trial; RDV = remdesivir; RT-PCR = reverse transcription polymerase chain reaction; SOC = standard of care; SpO_2 = oxygen saturation; SQ = subcutaneous; ULN = upper limit of normal; VL = viral load

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